JUN 1 1931

VOLUME 47 NUMBER 5

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Cambridge, Mass. WARFIELD T. LONGCOPE, Baltimore

J. H. MEANS, Boston WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

MAY, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

CONTENTS OF PREVIOUS NUMBER

APRIL, 1931. NUMBER 4

Normal, Absent and Pathologic Tonsils in Young Women: A Comparison of Histories. Ruby L. Cunningham, M.D., Berkeley, Calif.

Chronic Endemic Ergotism: Its Relation to the Vasomotor and Trophic Diseases. Julius Kaunitz, M.D., New York.

Multiple Pulmonary Abscesses Simulating Tuberculosis Caused by the Friedländer Bacillus. H. C. Sweany, M.D.; Asya Stadnichenko, A.B., and Karl J. Henrichsen, M.D., Chicago.

Streptococcic Septicemia with Vascular Lesions. J. M. Strang, M.D., and K. Semsroth, M.D., Pittsburgh.

The Closed Intestinal Loop: II. Observations on Dogs with Jejunal and Ileal Loops and Chemical Analyses of the Blood. George E. Burget, Ph.D.; Karl H. Martzloff, M.D.; Ross C. B. Thornton, B.S., and George R. Suckow, M.D., Portland, Ore.

Clear Fluid Test Meals (Water, Caffeine Solution, Alcohol) for Use in Fractional Gastric Analysis. A. L. Garbat, M.D., New York.

Experimental and Clinical Studies of Ergotamine: IV. The Effect of Ergotamine on the Basal Metabolism, Circulation and Blood Sugar of Normal Persons and of Patients with Thyrotoxicosis. John B. Youmans, M.D., and William H. Trimble, M.D., with the Technical Assistance of Helen Frank, B.A., Nashville, Tenn.

Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-Intestinal Tract: Report of Thirteen Cases. George B. Eusterman, M.D., and Paul A. O'Leary, M.D., Rochester, Minn.

II. The Galactose Tolerance Test in the Differential Diagnosis of Jaundice. Harry Shay, M.D.; Eugene M. Schloss, M.D., and Isadore Rodis, M.D., Philadelphia.

IV. The Diffusible Calcium of the Blood Stream in Tetany. Lewis Gunther, M.D., Los Angeles, and David M. Greenberg, Ph.D., Berkeley, Calif., with the Assistance of Mr. J. B. Dalton.

Book Reviews.

COPYRIGHT, 1931, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOLUME 47 MAY, 1931 NUMBER 5

NATURE OF THE SYMPTOMS ASSOCIATED WITH ESSENTIAL HYPERTENSION *

DAVID AYMAN, M.D.
AND
JOSEPH H. PRATT, M.D.
BOSTON

SOME PRESENT-DAY CONCEPTS OF THE SYMPTOMS

Two Groups of Symptoms.—With the increasing evidence [1] for the view [2] that essential arterial hypertension occurs first and organic changes in the arterioles are a sequence, there has developed the belief that these apparently successive pathologic states are accompanied by separate groups of symptoms. These may be termed the early and the late group of symptoms, the former being associated with the stage of pure arterial hypertension and the latter developing as a result of the vascular changes. Rolleston expressed the belief that the early and late symptoms, which differ in character, differ also in etiology.[3] It is important, therefore, for prognosis and study to distinguish between the so-called early and late symptoms. Sir Clifford Allbutt recognized this distinction, for, in his discussion of the symptom of dyspnea, he said that it "is a very late symptom. We are in the fifth act." [4] Of similar prognostic significance are nocturia secondary to renal insufficiency, vertigo secondary to cerebral sclerosis, etc., symptoms that are accompanied and probably caused by widespread arteriolar disease. The early symptoms, however, are not accompanied by such diffuse vascular disease, but occur in patients in whom, after clinical, laboratory and

* Submitted for publication, Sept. 11, 1930.

* From the Medical Clinic of the Boston Dispensary and the Division of Research.

1. Moschcowitz, E.: Hypertension with Minimal Renal Lesions, J. A. M. A. **77**:1075 (Oct. 1) 1921. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**:939 (June) 1928. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925. Evans, G.: Causation of Diffuse Hyperplastic Sclerosis, Brit. M. J. **1**:548 (March 31) 1923.

2. Allbutt, C.: Senile Plethora or High Arterial Pre sure in Elderly Persons, Tr. Hunterian Soc. **77**:38, 1895-1896.

3. Rolleston, H.: High Blood Pressure from the Clinical Aspect, Lancet **2**:1203 (Dec. 11) 1926.

4. Allbutt, C.: Diseases of the Arteries Including Angina Pectoris, London, 1915, vol. 1, p. 381; vol. 2, p. 61.

postmortem study, no adequate pathologic evidence is revealed to explain the symptoms or the associated elevation in blood pressure.[5] The character and etiology of the early symptoms—headache, dizziness, weakness, fatigability, irritability, nervousness, etc.—are the chief subjects of the present study. These symptoms will be termed the early symptoms associated with essential hypertension.[6] It is not correct to speak of them as the early symptoms of essential hypertension, for (1) arterial hypertension itself is only a symptom,[6] and (2) there is no evidence that the elevation in blood pressure produces these early symptoms.

A group of premonitory signs and symptoms that precede the so-called early symptoms has been described by several investigators. Alvarez [7] and Cummings [8] noted in young drafted men the frequent association of cyanosis of the extremities with elevated blood pressure. However, the diagnosis of essential hypertension was not established definitely in their patients. On the other hand, O'Hare, Walker and Vickers [9] and Ohler [10] studied the early life history of patients with long recognized primary hypertension. They found a significant incidence of vasomotor symptoms, such as flushing, blushing, cold, sweaty and cyanotic hands, frequent epistaxis, abnormal flowing at menstruation, migraine, fainting, dizzy spells and a type of personality characterized by morbid sensitiveness and a high-strung temperament. O'Hare found that one or more of these symptoms were noted, usually about the second decade of life, by 42 per cent of 300 hypertensive patients, compared to 23 per cent of 436 patients used as controls. Munk [11] stated the opinion that an increased excitability of the vascular system in the sense of a so-called sympathicotonia, or even a neurasthenic constitution, is commonly manifested in patients long before the arterial hypertension develops.

---

5. Moschcowitz (footnote 1, first reference). Bell (footnote 1, second reference). MacCallum, W. G.: Arteriosclerosis, Physiol. Rev. **2**:70, 1922. von Monakow, P.: Blutdrucksteigerung und Niere, Deutsches Arch. f. klin. Med. **133**:129 (Aug.) 1920. Pal, J.: Ueber Herzhypertrophie und Hypertonie, Med. Klin. **15**:662 (July 6) 1919. Münzer, E.: Gefaess-Sklerosen, Wien. Arch. f. inn. Med. **2**:1 (Dec.) 1920.

6. Rolleston (footnote 3). Christian, H. A.: Discussion, Am. Heart J. **2**:688 (Aug.) 1927.

7. Alvarez, W. C.: Surprising Frequency of Hypertension in a Group of Young Drafted Men, California State J. Med. **17**:367 (Oct.) 1919.

8. Cummings, R. S.: Study of One Hundred and Fifty Cases of Hypertension, California State J. Med. **17**:373 (Oct.) 1919.

9. O'Hare, J. P.; Walker, W. G., and Vickers, M. G.: Heredity and Hypertension, J. A. M. A. **83**:27 (July 5) 1924.

10. Ohler, W. R.: The Signs and Symptoms of Hypertension, Am. Heart J. **2**:609 (Aug.) 1927.

11. Munk, F.: Pathologie und Nierenkrankungen, Berlin, Urban & Schwarzenberg, 1925, p. 562.

General Characteristics of the Symptoms.—In addition to the conception of symptom groups, early and late, the understanding of the etiology necessitates a knowledge of the general character and distribution of the symptoms. There is widespread agreement in modern textbooks of medicine that the early symptoms are commonly "mistaken for manifestations of functional nervous disorders," [12] and that "the general symptoms often lead to a diagnosis of neurasthenia." [13] Allbutt [4] said that "to distinguish in a particular case between hyperpiesia (essential hypertension) in its earlier stages and neurasthenia may be a matter of some difficulty." Riseman and Weiss [14] also recently noted that in the psychoneuroses there are symptoms similar to those in arterial hypertension. It is also generally known that the early symptoms are referred to all parts of the body, so that no one symptom is typical of the disease. Kauffmann [15] and Kylin,[16] however, expressed the belief that the symptoms they most commonly encountered—dizziness, headache, palpitation, weight on the chest, rheumatoid pains, irritability, mild fatigue and sexual impotence—in their totality are typical of arterial hypertension even in its earliest stages, so that in many patients one may make the diagnosis merely on the history. The present study does not confirm this impression.

Previous Conceptions of the Etiology of the Early Symptoms.—Finally, before presenting our own observations, three views concerning the etiology of the early symptoms will be discussed, having been selected because of their close adherence to the modern concept of essential hypertension.

One view is that the early symptoms are produced solely by the elevation in blood pressure. The evidence against this opinion may be summarized as follows: 1. There is apparently no close correlation between the onset, the number or severity of the symptoms and the level of the blood pressure. 2. The symptoms may frequently be relieved with little or no change in the level of the blood pressure.[17] 3. Many

12. Goodridge, M.: Essential Hypertension, in Cecil, R. L.: Textbook of Medicine, Philadelphia, T. Nelson & Sons, 1927, p. 1060.

13. Mosenthal, H. O.: Essential Hypertension, in Nelson: Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1927, vol. 4, p. 515.

14. Riseman, J. E. J., and Weiss, S.: The Symptomatology of Arterial Hypertension, Am. J. M. Sc. **180**:47 (July) 1930.

15. Kauffmann, F.: Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, München. med. Wchnschr. **71**:1230 (Sept. 5) 1924.

16. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926, pp. 65, 36 and 103.

17. Ayman, D.: An Evaluation of Therapeutic Results in Essential Hypertension, J. A. M. A. **95**:246 (July 26) 1930.

hypertensive patients have no symptoms. In this regard, one should remember that different individuals vary in their susceptibility to stimuli;[18] that which may produce severe headache in some people seems to have no effect on others. 4. Many similar symptoms occur in both arterial hypertension and arterial hypotension, so that they probably are not due to the increase or decrease of the blood pressure alone.[3]

The second concept considers both the symptoms and the elevation in blood pressure to be due to a toxemia.[3] The belief that such a toxemia may be of bacterial origin is supported by the studies of Koessler, Lewis and Walker,[19] who found in bacterial filtrates substances that, when injected into animals, caused a marked rise of blood pressure. The possibility of a metabolic toxemia has been shown by Major.[20] He observed that when methyl guanidine sulphate was injected intravenously into dogs, it produced a marked elevation of blood pressure. In the blood of hypertensive subjects, he found an increased amount of a substance that he believed to be guanidine.

The third hypothesis, as proposed by Pal,[21] Kylin[22] and Laufer,[23] is that the symptoms are caused by a primary disturbance of the vegetative nervous system, a disorder that they termed vegetative neurosis, angiotonic neurosis, etc. However, the authors of these terms did not state or imply that their so-called neurosis is of psychic origin. Kylin cited[22] the following evidence: 1. There is a great variability in the blood pressure, which he said can be explained only as a nervous vasomotor disturbance and not as an organic contraction of the vessels. 2. The decreased tolerance for carbohydrates in essential hypertension suggests a disorder of the vagosympathetic system. 3. The marked reaction after the injection of epinephrine indicates a sensitiveness of the sympathetic nervous system. 4. The general symptoms of nervousness, so common in essential hypertension, cannot be distinguished from those of other nervous disorders.

---

18. Libman, E.: Observations on Sensitiveness to Pain, Tr. A. Am. Physicians **41**:305, 1926.

19. Koessler, K. K.; Lewis, J. H., and Walker, J. A.: Pharmacodynamic Actions of Bacterial Poisons, Arch. Int. Med. **39**:188 (Feb.) 1927.

20. Major, R. H.: The Possible Relationship Between Guanidin and High Blood Pressure, Am. J. M. Sc. **170**:228 (Aug.) 1925.

21. Pal, J.: Arterieller Hochdruck, Klin. Wchnschr. **2**:1151 (June 18) 1923.

22. Kylin, E.: Ueber die essentielle Hypertonie als Teilsymptom bei einer funktionellen Krankheit, Acta med. Scandinav. **59**:590, 1923.

23. Laufer, O.: Ueber Subtonin (Löwenstein) nebst Bemerkungen über die Behandlung des arteriellen Hochdrucks, Med. Klin. **23**:1150 (July 29) 1927.

PRESENT STUDY

We have already noted the common statement of clinical investigators that the early symptoms associated with essential hypertension closely resemble those of the psychoneuroses. Because of this similarity, the problem of the relation of the symptoms presented by hypertensive patients to those observed in the psychoneuroses seemed worthy of study. The possibility of a psychic origin for the early symptoms associated with essential hypertension was suggested by the clinical experience of one of us (J. H. P.). This idea was further encouraged by an earlier study, in which[17] 82 per cent of forty hypertensive patients were definitely relieved of their symptoms by suggestion. Added support for this opinion was afforded by the widespread belief that, as in the psychoneuroses, the greatest relief from the symptoms of which the hypertensive patients complain may be obtained by the removal of worries, fears and other disturbances in the psychic sphere.

The first step was to study separately the symptoms associated with essential hypertension and those of the psychoneuroses.

THE SYMPTOMS ASSOCIATED WITH ESSENTIAL HYPERTENSION

Method and Material.—The data were obtained by: (1) analyzing 100 unselected outpatient records of hypertensive cases, and (2) supplementing 53 of these records with a personal study of the patients. The 100 patients investigated had visited the clinic over periods ranging from one to seventeen years, while the known duration of their hypertension was from one to ten years. The minimal criteria[24] in this study for the diagnosis of essential hypertension were: (1) many readings of the blood pressure of 160 mm. of mercury or more, and (2) the absence of evidence of nephritis on chemical and microscopic examination of the urine, normal dilution, concentration and phenolsulphonphthalein tests of the kidneys. There were 17 men, with an average age of 55, and a range in age between 42 and 70; there were 83 women, with an average age of 52, and a range in age between 32 and 74.

Since there were 45 women in the age group of from 40 to 55 years, it might be contended that their symptoms were related to the menopause. The following facts make this idea improbable: 1. Of the fifty-three patients studied personally, there were twenty-five whose symptoms had begun before the age of 35 (chart 1), whereas the menopause occurs before 35 and after 55 in less than 0.7 per cent of women.[25] 2. Thirty-nine of the fifty-three patients had symptoms for

24. Ayman, D.: Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94**:1214 (April 19) 1930.

25. Graves, W. P.: Gynecology, ed. 2, Philadelphia, W. B. Saunders Company, 1918, pp. 19, 22 and 128.

more than ten years (chart 1), whereas it is stated [25] that (*a*) the menopausal organic changes extend over a period ranging from several months to two years at the most, and (*b*) the average duration of symptoms after artificial menopause is from two to three months. 3. Most of the women patients gave no history of a recent or present menstrual disturbance. 4. There were identical symptoms in the hypertensive men of the same age group.

Frequency of Symptoms.—The accompanying table shows the incidence of the symptoms in 100 patients with essential hypertension. These figures are derived not only from the symptoms complained of at the

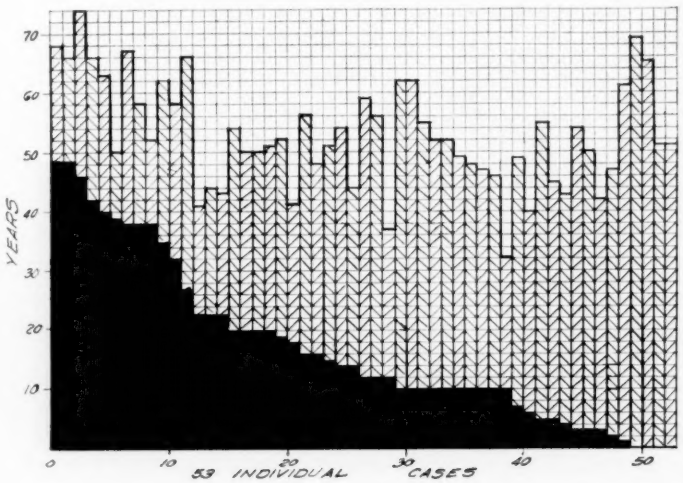

Chart 1.—The individual duration of the symptoms in fifty-three hypertensive patients. Each vertical hatched column is to be considered continuous with a vertical black column directly below it. The total vertical height of each column (black plus hatched) represents the age of the individual patient. The individual vertical black column represents the duration of the symptoms in each case. For example, the first column represents a patient 68 years of age, whose symptoms have existed for forty-eight years, having commenced at the age of 20 years.

initial visit to the clinic, but from those which, in the recorded absence of demonstrable organic disease, were present previously or subsequently to the first visit. Hence our figures differ from the results of Kauffmann [15] and Schultz and Biehn,[26] who apparently tabulated only

26. Schultz, J. H., and Biehn, W.: Ueber die Häufigkeit einzelner wichtigerer Klagen und anamnestischer Angaben bei Kranken mit arterieller Hypertension, Deutsche med. Wchnschr. **51**:25 (Jan. 2) 1925.

the symptoms noted at the time of observation. Our figures actually represent the totality of the symptoms in 100 patients that have occurred during the recognized span of the hypertension, or that can be shown by the history to have existed more or less continuously from an earlier time to the time of writing. The symptoms utilized were not transitory, but lasted for days, weeks, months and years, and were often severe. Chart 1, obtained in a manner similar to table 1, represents the total duration of the symptoms (present illness) in the fifty-three patients who were studied personally.

General Characteristics.—The accompanying table and chart 1 illustrate three general characteristics of "hypertensive" symptoms: 1. These symptoms are usually multiple and widespread, being referred to almost

Frequency of Individual Symptoms in One Hundred Patients with Essential Hypertension

	Percentage		Percentage
Headache	72	Epigastric fulness	30
Pain	67	Anorexia	28
"Nervousness"	67	Heartburn	24
Dizziness	66	Nausea	21
Fatigue and weakness	65	Palpitation	18
Insomnia	63	Pain over cardiac area	15
Constipation	57	Vomiting	14
Fatigue	55	Tremors	12
Local or generalized flushing	54	Choking sensation	12
Weakness	38	Cough	9
Paresthesias	38	Unpleasant taste in the mouth	7
Eructations of gas	37	Fainting	6
Shortness of breath	34	Loss of weight	6

every part of the body. 2. There is a high frequency of certain symptoms, such as headache, pain, "nervousness," dizziness and fatigue. 3. The duration of the symptoms (present illness) is unusually long. Chart 1 shows the duration of the symptoms in the fifty-three patients who were studied personally. Thirty-nine patients had symptoms over a period of more than ten years, twenty-six for more than fifteen years and ten for more than thirty-five years.

That only 4 of the 100 patients were symptomless is probably due to the fact that in these patients the hypertension was found in the course of examination for other maladies.

SYMPTOMS OF THE PSYCHONEUROSES

Most authorities agree that the psychoneuroses are psychogenic disorders.[27] They arise from faulty adaptations to the difficulties of life. There is a resultant emotional perturbation which expresses itself

27. Ross, T. A.: The Common Neuroses, New York, Longmans, Green & Company, 1924. Déjerine, J., and Gauckler, E.: The Psychoneuroses, Philadelphia, J. B. Lippincott Company, 1915.

physically by symptoms. The development of the symptoms depends on the intensity and duration of the difficulties and on the individual susceptibility. Whereas a simple rebuke may cause brooding and headache in highly sensitive and susceptible persons, it requires great life and death conflicts, such as those in the front line trenches, to produce "shell-shock" psychoneuroses in others. There may then result a functional disorder of any mechanism, organ or region of the body.

The diagnosis rests on three facts: (1) The presence of symptoms, which are often multiple, widespread and usually not conforming in their entirety to any other clinical picture. With these are usually associated symptoms and signs of emotional instability such as irritability, inability to concentrate, excitability and attacks of weeping. (2) Negative results of a physical examination. (3) Elicitation from the patient of the fact that a period of important emotional stress preceded the development of symptoms. The diagnosis may be corroborated further by long clinical observation and psychotherapeutic success.

Methods and Data.—The symptoms of psychoneurosis were studied in a group of fifty psychoneurotic patients, observed personally, who had been coming to the clinic for many years because of the somatic symptoms of neurasthenia, anxiety neurosis or hysteria. These patients, with normal blood pressure, were of the same age as the hypertensive patients. The average age was 48, with a range in age between 35 and 66. The data were obtained in the same way as in the hypertensive group. In twenty-four of the fifty, the onset of symptoms occurred before the age of 35 (chart 2). This fact, together with evidence similar to that already presented for the hypertensive group, makes unlikely a menopausal origin of the symptoms.

COMPARISON OF SYMPTOMS OF BOTH DISEASES

Chart 2 illustrates the duration of the symptoms in the fifty psychoneurotic patients. Twenty-nine of the fifty patients had their symptoms for ten years or more, eighteen for fifteen years or more and eight for twenty years or more. The close similarity in the duration of the symptoms in essential hypertension and in the psychoneuroses is strikingly apparent on comparison of charts 1 and 2.

In chart 3 the frequency, multiplicity and widespread distribution of the symptoms in the fifty psychoneurotic patients are illustrated by white hatched columns, and are compared with the same aspects of the symptoms in fifty patients with essential hypertension (black columns). Here again the striking agreement is evident.

However, this close similarity between the two diseases was found not to be limited to the general features of the symptoms, but to be

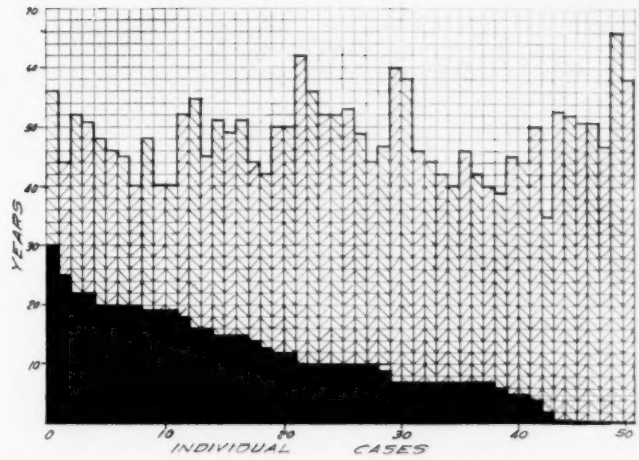

Chart 2.—The individual duration of the symptoms in fifty psychoneurotic patients with normal blood pressure. The black and hatched columns are to be interpreted in the same way as in chart 1.

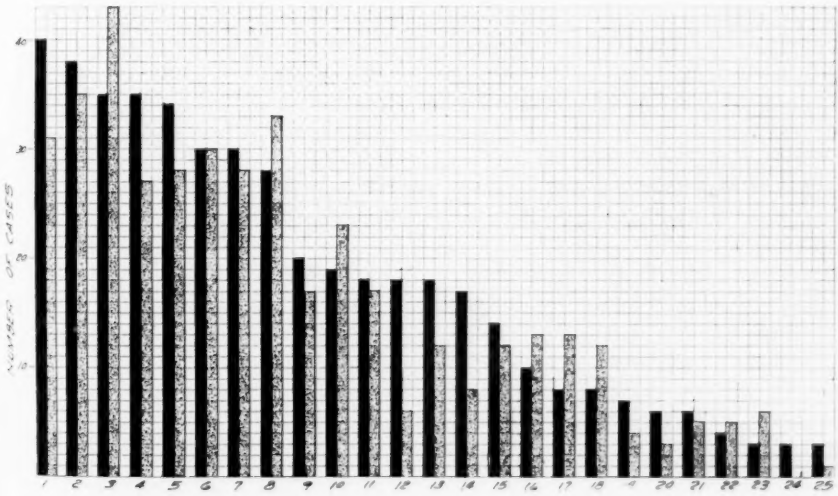

Chart 3.—Comparison of the frequency of the individual symptoms in fifty patients with essential hypertension (black columns) and fifty patients with psychoneurosis (peppered columns). The columns labeled *1* represent the symptom irritability, and indicate that irritability was a complaint in forty of fifty hypertensive patients, while it was present in thirty-two of fifty psychoneurotic patients; column *2* represents headache; *3*, pain; *4*, dizziness; *5*, insomnia; *6*, fatigue; *7*, local or generalized flushing; *8*, constipation; *9*, weakness; *10*, paresthesias; *11*, eructations of gas; *12*, heartburn; *13*, shortness of breath; *14*, epigastric fulness; *15*, anorexia; *16*, nausea; *17*, palpitation; *18*, pain over cardiac area; *19*, vomiting; *20*, tremor; *21*, choking sensation; *22*, cough; *23*, loss of weight; *24*, fainting, and *25*, unpleasant taste.

manifest in the character of the individual symptoms. For example, fatigability or a feeling of weakness was one of the most common symptoms encountered in the hypertensive group. Its usual intensity was so great that the patients frequently termed it "exhaustion." It was brought on by slight exertion or occurred when the patient was at rest, and frequently was not relieved by sleep. Its exact counterpart was regularly met with in the same frequency among the fifty psychoneurotic patients (chart 3). Fatigability, in fact, is one of the chief characteristics of the psychoneuroses. It is rarely found to such a degree in ambulatory patients with any other chronic disease, such as pulmonary tuberculosis. We shall also consider the symptoms headache and dizziness. We have been unable to find among the hypertensive patients a type of headache that might be termed characteristic; the patients described this symptom variously—as heaviness, emptiness, fulness, the feeling as if there were a band around the head, soreness, burning, throbbing, etc., occurring at any time of the day and in any part of the head. Dizziness was also described variously, from a feeling of light-headedness to true vertigo. The variability of the headaches and of the dizziness among our hypertensive patients is in conformity to what one sees in psychoneurotic persons.[27] It should be pointed out that headache and dizziness occurred with slightly greater frequency among the hypertensive persons in our small series than among the psychoneurotic ones with normal blood pressure. The frequency is seen in chart 3. A similar comparison of all the other symptoms of the two diseases in the fifty patients showed a striking parallelism. The same symptoms occurred in both in about the same frequency.

THE EMOTIONAL LIVES OF HYPERTENSIVE PATIENTS

Even if the symptoms of both diseases have a marked likeness in their incidence and in their general and individual characteristics, it still remains to be shown that they have a common origin. Since the inception of the symptoms of the psychoneuroses is considered the result of a faulty adaptation to an emotional strain, and was so found in our fifty cases, it remained to investigate this possibility in the hypertensive group. This was studied in fifty-three hypertensive patients. A detailed history of the patients' emotional lives was recorded. It was found that many of them had experienced emotional disturbances resulting from faulty adaptation to marked psychic and environmental difficulties. These emotional burdens were found to extend back to youth in many patients and seemed to be of a magnitude surpassing those experienced by most normal persons. Roughly, personality studies of these patients showed that throughout their lives they responded with a marked emotional reaction to the usual incidents of life. In many cases, how-

ever, they had to face difficult situations. There seemed to be an abnormally high percentage of the patients who said they had had an "unhappy life." It was found, further, that the symptoms followed emotional difficulties. The following example illustrates briefly the type of emotional history obtained.

M. L., aged 41, a widow, whose blood pressure was 210 systolic and 110 diastolic, said that her life had been unhappy since the age of 13. She was averse to discussing the details of her life. At the age of 16 (1905), in Russia, her mother forced her to marry a man with whom she was hardly acquainted. He turned out to be a drunkard. They had three children, and then her husband deserted her. She took one of her children and went to England eighteen years before examination (1912), and while she was there she had a "nervous breakdown," the chief symptom of which was choking spells. Shortly afterward she left for the United States. She had never again seen her other two children, who lived with a wealthy brother in Russia. Her husband joined her again, but she was forced to leave him because of his abuse. The only child born in the United States had moved to a distant part of the country and had paid no attention to her. Her husband had died in an accident nine years previously, and she had no regrets. She had been living alone in a single room for seven years. (She cried often during the foregoing recital.)

Further analyses showed that not only did the original onset of symptoms in these hypertensive patients follow great emotional upsets, but in later life the recurrences of the symptoms were closely associated with periods of definite mental agitation, as illustrated in the following case.

The blood pressure of the patient had varied from 248 systolic and 120 diastolic to 180 systolic and 110 diastolic since she was first observed on Oct. 28, 1927. On March 7, 1929, the patient came to the clinic complaining of fatigue, inability to sleep and nervousness. She had been free from symptoms for a long period, but six weeks previously her present symptoms gradually developed and since had increased in intensity. Physical examination revealed no abnormality except the elevated blood pressure.

The patient's husband had been laid off from work six weeks previously, and their savings were so scanty that they were already in difficult financial straits. For the past four weeks he had been confined to the house by a cold. His irritability and continual presence at home disturbed the patient.

It is not meant that every hypertensive patient has had great emotional difficulties and an unhappy life. A few of our patients yielded no such information, whether because of reticence or not we do not know. In such patients it was often noted that they had no great sorrows or anxieties, but a life continually full of small annoyances. They seemed to be persons who worried about trivialities. They were frequently the ones with a family history of vascular disease. Here again it is to be noted that our cases were all dispensary cases; yet there

is a resemblance between this last group of patients and the type described by Moschcowitz,[28] which was met with in private practice.

So far it may be summarized that the early symptoms associated with essential hypertension could not be differentiated from those of the psychoneuroses, either by their incidence or by their general and individual characteristics; that in both groups of patients no abnormality on physical or laboratory examinations could be found adequate to explain the symptoms, and, finally, that in both groups of patients a significant degree of maladjustment to emotional difficulties was found to explain the development of symptoms at the time they appeared.

There is available, however, some added evidence that the early symptoms associated with essential hypertension are due not to organic changes, but to the emotional maladaptation of the patient. This evidence resides in the results of treatment. If the early symptoms associated with essential hypertension are of psychoneurotic nature, they should respond to three forms of therapy usually effective for the symptoms of psychoneurotic patients: (1) removal of environmental difficulties or adjustment to them, (2) sedatives and (3) suggestion. This has been found to hold true for our patients.

In regard to the removal of environmental difficulties or more adequate adaptation to them, it is probably the form of hypertensive therapy that has the most widespread support.[29]

The successful use of sedatives in the symptomatic therapy for essential hypertension has also received wide mention.[30]

Evidence for the successful effect of suggestion on "hypertensive" symptoms exists in an aforementioned investigation by one of us.[17] In this study it was found that in 82 per cent definite symptomatic relief was obtained in a group of forty patients treated by simple suggestion, which consisted of prescribing a few drops of dilute hydrochloric acid daily. This impressively tasting medicine, undoubtedly nonspecific, coupled with continual encouragement, was used over periods of from one week to four months with a resultant success in 82 per cent. It

28. Moschcowitz, E.: Hypertension: Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, Am. J. M. Sc. **158**:668 (Nov.) 1919.

29. Mosenthal, H. O.: The Treatment of Essential Hypertension, J. A. M. A. **91**:698 (Sept. 8) 1928. Fahrenkamp, K.: Die psycho-physischen Wechselwirkungen bei den Hypertonierkrankungen, Stuttgart, Hippokrates, 1926. Goldscheider, A.: Ueber Wesen und Behandlung der Hypertension des Blutdrucks, Ztschr. f. ärztl. Fortbild. **23**:1 (Jan.) 1926.

30. O'Hare, J. P.: Treatment of Hypertension, Am. Heart J. **2**:510 (June) 1927. Henius, K.: Brombehandlung bei Hypertonie, Klin. Wchnschr. **3**:958 (May 20) 1924.

is only from such a point of view that one can interpret many of the last decade's 200 or more successes [17] in the therapy for essential hypertension.

While it seems reasonable to conclude that the early symptoms associated with essential hypertension are probably of psychic origin, the fundamental mechanism is not clear. Constitutional influences, endocrine products and possibly other factors may contribute to lessen the hypertensive patient's psychic and physical capacity for withstanding the stress and strain of life.

SUMMARY

Clinical observations are presented to support the view that the early symptoms associated with essential hypertension are of psychic origin.

484 Commonwealth Avenue.
270 Commonwealth Avenue.

THE GAIN IN BODY WEIGHT ASSOCIATED WITH REMISSIONS IN PERNICIOUS ANEMIA*

JANET M. VAUGHAN, B.M., B.Ch. (Oxford)
British Medical Research Council Fellow
LONDON, ENGLAND

In 1927, Minot and Murphy [1] drew attention to the striking gain in body weight observed in patients with addisonian pernicious anemia who were given liver therapy, and this observation has been borne out by the majority of subsequent reports. This gain in weight occurs whether whole liver or liver extract is used. Meulengracht and Holm [2] recently analyzed a series of thirty-six cases, with special reference to the gain in body weight, and showed that the average gain over a period of from one to two years was 54 pounds (24.5 Kg.), showing no appreciable difference in patients receiving extract or whole liver or a combination of the two. I [3] reported the case of one patient treated with whole liver who gained as much as 20 pounds (9 Kg.) in one month. Wyckoff and Bloomfield [4] cited the cases of two patients who were given extract only, and who gained 13.5 and 91 pounds (6.3 and 41.3 Kg.) respectively.

There is a tendency to consider that this gain in weight is dependent on the action of the liver or of the liver extract itself rather than on the improvement in the blood and the general condition of the patient. However, in 1920, Minot,[5] reviewing the symptomatology of pernicious anemia, stated that "loss of weight not infrequently occurs with relapses, to be regained in remissions," and quoted the case of a man weighing 180 pounds (81.6 Kg.), who in a series of relapses lost between 35 and 50 pounds (15 and 22 Kg.) on each occasion, gaining back his original weight during a remission. Such a gain of approximately 50 pounds is in striking accord with the average figure already quoted from Meulengracht's series of cases in which treatment with liver was used.

* Submitted for publication, Aug. 5, 1930.

* From the Thorndike Memorial Laboratory, Boston City Hospital.

1. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia with Liver or an Effective Fraction of Liver: Study of 105 Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

2. Meulengracht, E., and Holm, S.: Vegtførøgelsen ved leverbehandling af perniciøs anämie, Ugesk. f. laeger **91**:479 (June 6) 1929.

3. Vaughan, J. M.: The Liver Treatment of Anemias, Quart. J. Med. **23**:213 (Jan.) 1930.

4. Wyckoff, H. A., and Bloomfield, A. L.: Liver Extract in Pernicious Anemia, California & West. Med. **30**:225, 1929.

5. Minot, G. R.: Clinical Discussion of the Anemias, Oxford Medicine, New York, Oxford University Press, 1920, vol. 2.

It would appear, therefore, that liver per se, cannot be considered to exert any peculiar effect on the weight of patients with addisonian pernicious anemia, since equally striking changes were observed before its introduction as a therapeutic agent. Such changes occur coincident with an improvement in the blood picture, independent of the exciting cause of a remission.

The following factors might on theoretical grounds be responsible for the increase in body weight: (1) increased caloric intake dependent on the improved appetite, (2) retention of fluid leading to edema and (3) some alteration in metabolism similar to that occurring in myxedema.

The object of the present investigation was to determine as far as possible if one or more of these factors were involved.

METHODS

Twelve cases of addisonian pernicious anemia were followed during the last year. They showed no severe renal damage, as evidenced by the absence of albumin and casts from the urine and a blood pressure within normal limits. The patients were also being studied for special purposes unconnected with the present inquiry. They were given liver preparations by intravenous administration, as recently reported by Cohn, McMeekin and Minot,[6] or digestion mixtures of beefsteak and gastric juice, as described by Castle and his associates,[7] to initiate a remission. Improvement was then maintained by commercial extract.

To determine how far the caloric intake was of importance, daily records were kept of the exact value of the food taken. The diets were low in protein, as no red meat was given, in order to insure that the effect of any treatment should be uncomplicated by improvement possibly due to the ingestion of such meat. In calculating the value of the protein in any diet, allowances were made for the amount fed in the digestion mixtures. In all patients, therefore, except 1 and 12, the daily intake of protein did not exceed 50 Gm., the average being 42 Gm.

Seven patients received a strict basal diet, allowing 25 calories per kilogram of body weight. Two patients were given a diet well above their caloric requirements. Three patients received first a basal ration, and when after several weeks they showed no gain in weight in spite of improvement in the blood picture, they were given one of higher caloric value during the subsequent period.

In order to ascertain whether the retention of fluid might be responsible for the gain in weight, records were kept of the total excretion of urine and intake of fluid during twenty-four hour periods. It is recognized that such determinations

6. Cohn, E. J.; McMeekin, T. L., and Minot, G. R.: The Nature of the Material Effective in Pernicious Anemia, J. Biol. Chem. **87**:49 (June) 1930.

7. Castle, W. B., and Locke, E. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, J. Clin. Investigation **6**:2 (Aug.) 1928. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients With Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748 (Dec.) 1929. Castle, W. B., and Townsend, W. C.: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, ibid., p. 764.

are subject to considerable error, as DuBois [8] pointed out, but it was thought that they might give some indication as to whether any considerable quantity of fluid was retained at any time and provide at least comparative figures.

Determinations of the basal metabolic rate were made at intervals, a Benedict-Roth recording apparatus being used.

RELATION OF GAIN IN WEIGHT TO CALORIC INTAKE

Table 1 shows the relation of the caloric intake to the gain in weight and total red blood cell count in twelve cases of pernicious anemia. Only

TABLE 1.—*Relation of Changes in Body Weight to Caloric Intake, Red Blood Cell Count and Treatment*

	Gain or Loss of Body Weight in Pounds After Treatment			Red Blood Cell Count in Millions per C.Mm.			
Patient	Basal Diet* from 4 to 15 Weeks	Ample Diet* from 3 to 5 Weeks	From 2 to 24 Weeks After Leaving Hospital*	Before Treatment	On Leaving Hospital from 2 to 15 Weeks After Beginning Treatment*	From 2 to 24 Weeks After Leaving Hospital	Treatment
1	−9.75	.....	− 4.0	1.4	3.0	3.6	Digestion mixture, commercial extract
2	−3.0	.....	− 3.0	1.6	3.1	4.4	Preparation given intravenously, commercial extract
3	−3.0	.....	+ 8.0	2.6	3.5	4.2	Preparation given intravenously, commercial extract
4	−0.5	.....	+ 5.5	1.3	2.6	4.1	Preparation given intravenously, commercial extract
5	−2.0	.....	+ 4.5	1.2	2.9	4.7	Digestion mixture, commercial extract
6	−7.0	.....	.....	2.6	3.9	4.7	Digestion mixture, commercial extract
7	+2.5	.....	+ 4.0	1.9	2.7	4.7	Digestion mixture, commercial extract
8†	.....	+3.00	.....	2.1	4.4	...	Digestion mixture, commercial extract
9	−3.5	−0.75	+ 7.0	1.7	4.6	4.4	Digestion mixture, commercial extract
10	−2.75	+0.75	+ 4.5	2.6	3.9	4.7	Commercial extract
11	.....	+10.25	+18.5	1.4	3.8	4.7	Digestion mixture, commercial extract
12	.....	+4.25	+ 7.0	1.1	3.3	4.1	Digestion mixture, commercial extract

* The periods of time must not be regarded as those normally required to achieve the degree of improvement noted either in weight or in total red cell count, since the majority of the patients were being studied for special purposes. The materials tested varied considerably in potency, and the treatment was not always continuous.

† Too ill to weigh on entry.

one of seven patients on a strict basal diet, when he left the hospital, showed a gain over his weight before treatment. Six patients had a loss of weight varying from 9.75 to 0.5 pounds (from 4.4 to 0.2 Kg.) Three patients who received first a basal and then an increased diet showed an increase in weight on the latter above that on the basal diet. Two patients who had had a diet above their caloric requirements through-

8. DuBois, E. A.: Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1924.

out treatment showed a definite gain in weight: 10.25 pounds (4.7 Kg.) in patient 11, in thirty-four days, and 4.25 pounds (2 Kg.) in patient 12 in eight days. The caloric intake in the first of these patients is difficult to calculate accurately, as he had difficulty in retaining all the beefsteak mixture fed by nasal tube. The daily excess over his basal requirements was approximately 700 calories. Patient 12 did not vomit, and his excess intake was approximately 1,000 calories. Therefore, four of five patients gained weight on an ample diet as opposed to the gain in weight of one of seven patients on a basal diet.

A more careful analysis of the weight during treatment is made in table 2, and shows that an almost constant fluctuation occurs in the body weight of the patient with pernicious anemia during a remission. This fluctuation is closely associated with changes in the red blood cells and,

TABLE 2.—*Relation of Changes in Body Weight to Intake of Fluid and Output of Urine*

	Gain or Loss of Body Weight in Pounds				Daily Average Gain or Loss of Body Fluid in Cc.			
Patient	At Time of Reticulocyte Rise	Following Reticulocyte Rise	At Time of Discharge from Hospital	From 2 to 24 Weeks After Discharge from Hospital	Period I at Time of Reticulocyte Rise	Period II Following Reticulocyte Rise	Period III During Second Gain in Weight	Edema
1	+7.25	—18.25	+1.25	+5.75	+670	+458	+360	+
2	+2.75	— 5.75	No change	No change	+ 62	—353	.....	Not noted
3	—2.0	— 5.5	+ 4.5	+11.0	Record not complete		.....	Not noted
4	+4.0	— 7.5	+ 3.0	+ 6.0	+598	+ 67	+180	+
5	+4.5	— 7.0	+ 0.5	+ 6.5	Record not complete		.....	Not noted
6	—1.5	— 7.0	+ 1.5	.....	+249	—169	.....	+
7	+4.0	— 3.0	+ 1.5	+ 1.5	+557	—344	—193	+
8	.....	— 5.0	+ 8.0	.....	+250	— 82	—294	Not noted
9	No change	— 5.5	+ 4.25	+ 8.25	—463	—151	—202	Not noted
10	.....	— 2.75	+ 3.5	+ 3.75	.....	—186	.....	Not noted
11	+1.0	Weight rose steadily	+ 9.25	+ 8.25	+ 60	.....	—102	Not noted
12	+8.0	— 5.0	+ 1.25	+ 2.75	+255	—390	— 40	+

as will be shown later, with alterations in the fluid balance. It naturally divides the time of recovery into three distinct periods. In the first period, lasting from the onset of treatment to the peak of the reticulocyte response, there was a gain in weight in seven of the ten cases in which the records were complete. The maximum gain was 7.25 pounds (3.3 Kg.) in patient 1, who was receiving a basal diet at this time. Two patients showed a slight loss of weight, and in one the weight remained constant.

The second period occurred during the days following the peak of the reticulocyte rise. It was characterized by a loss of weight of from 18.25 to 2.75 pounds (from 8.3 to 1 Kg.), occurring in all patients except patient 11, who was receiving an ample diet. The weight started to fall immediately after the peak of the rise and continued to fall for a period varying from four to twenty-one days.

During the third period there was a gain in weight in all patients except patient 2, whose weight remained constant. With one exception, however, the gain in weight in the patients receiving a basal diet, calculated from the original weight before treatment, did not exceed this level. In patients 9 and 10 the gain in weight occurred only after the basal diet had been increased. These observations, together with the fact that all except two patients gained weight in the weeks following their discharge from the hospital, when presumably they led more normal lives with no control exerted on their diet, suggest that caloric intake plays an important rôle in the gain in weight.

It has been suggested [9] that the effect of certain liver extracts in lowering the blood sugar, as described by Murphy and Blotner,[10] may account in part for the increased caloric intake through increasing appetite. Riddle,[11] however, stated that the fall in the level of the blood sugar during fasting is dependent on the metabolic adjustment accompanying remission rather than on the direct influence of liver or of liver extract on the level of the blood sugar. The one case he reported in which observations were made during a spontaneous remission showed 91 mg. of sugar per hundred cubic centimeters as its lowest figure, which is hardly sufficient to account for a very appreciable increase in appetite.

It has also been suggested that the high content of vitamin B in both liver and certain liver extracts may contribute to the improved appetite and, therefore, to the increased caloric intake.

Since, however, improved appetite and gain in weight occur in spontaneous remissions, it seems unlikely that vitamin B is responsible for such changes.

RELATION OF GAIN IN WEIGHT TO INTAKE OF FLUID AND OUTPUT OF URINE

The analysis of the relation of intake of fluid and output of urine to gain in weight, which is made in table 2, shows, however, that possibly retention of fluid may play a part in the fluctuations observed in the weight during a remission. Variations in the fluid balance are seen to occur in the same periods as do alterations in body weight.

In the first period, all patients in whom the records were complete, except patient 9, who alone did not gain weight, showed an average daily excess of intake of fluid over output of urine. In three patients gross

9. Minot, G. R.: The Treatment of Pernicious Anemia with Liver or with an Effective Fraction of Liver, Tr. A. Am. Physicians **49**:144, 1927.

10. Murphy, W. P., and Blotner, H.: The Effect of Liver Feeding on the Blood Sugar, J. Clin. Investigation **4**:440 (Aug.) 1927.

11. Riddle, M. C.: The Blood Sugar During Remission in Pernicious Anemia, Ann. Int. Med. **3**:1097 (May) 1930.

edema developed at this time, and in two others edema present at the time of admission became worse.

During the second period, the output of urine exceeded the intake of fluids in seven of nine patients. There was, therefore, a complete reversal of the fluid balance associated with a similar reversal in body weight. The edema during this period decreased rapidly.

In the third period, when all patients gained weight, the fluid output still exceeded the fluid intake except in patients 1 and 4, in whom the edema, however, continued to decrease.

It is recognized that the measurement of the intake and output of fluid as an indication of the retention of water by the body is unsatisfactory. No stress is laid on the actual figures here recorded, but the association of gross edema with the period of apparent retention of water and its diminution or complete disappearance during the second period suggest that there is considerable significance in the results obtained.

Characteristic changes in the excretion of water have long been recognized in pernicious anemia. Cabot [12] noted edema in 69 per cent of his patients. Mosenthal,[13] Stieglitz [14] and Christian [15] found a change in excretion as evidenced by a tendency to fixation of specific gravity without accompanying polyuria and a relative increase in the excretion of urine during the night. Saltzman [16] also commented on the fixation of specific gravity. Meulengracht and his associates [17] found that the inability to excrete large quantities of ingested fluid shown by a patient during a relapse is recovered during a remission. Kofanov [18] more recently repeated and confirmed these results on patients receiving liver, but did not correlate his observations with the reticulocyte crisis. Such changes are reported not to occur in either chlorotic or posthemorrhagic anemias.

---

12. Cabot, R. C., in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 5.

13. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluids, Salts and Nitrogen and the Specific Gravity of the Urine, Arch. Int. Med. **15**:733 (Nov.) 1915.

14. Stieglitz, E. J.: Disturbances of Renal Function in Pernicious Anemia, Arch. Int. Med. **33**:58 (Jan.) 1924.

15. Christian, H. A.: Renal Function in Pernicious Anemia, Arch. Int. Med. **18**:429 (Oct.) 1916.

16. Saltzman, F.: Kliniska och patologisk-anatomiska iakttageler rörande njurarnas förhållande vid den perniciösa anemien, Finska läk-sällsk. handl. **61**: 157, 1919.

17. Meulengracht, E.; Iversen, P., and Nakazawa, F.: Pernicious Anemia: Edema and Reduction in Excretion of Water, Arch. Int. Med. **42**:425 (Sept.) 1928.

18. Kofanov, J.: Beiträge zum Wasserstoffwechsel bei perniziösen Anämie, Wien. Arch. f. inn. Med. **19**:303, 1930.

Much discussion has arisen as to the cause of this disturbance in urinary excretion. Is the kidney itself at fault or are extrarenal factors responsible? Stieglitz [14] and Saltzman [16] emphasized the importance of anatomic lesions in the kidney, but the usual tests of renal function other than the excretion of water show little impairment. Albumin in the urine is not a constant feature. Cabot [12] reported a trace present in 40 per cent of his cases, while Meulengracht [17] found it to be a transitory phenomenon only in 29 per cent of his cases. The excretion of thiosulphate was normal in the majority of Meulengracht's patients, and the same was found by Christian [15] using phenolsulphonthalein. The evidence in respect to the retention of urea is contradictory. Gettler and Lindeman [19] reported retention in 50 per cent of their cases, but they did not correlate their observations in any way with the age of the patient. Meulengracht,[17] on the other hand, found it in only one of his patients, in whom cardiac decompensation was present. It would appear, therefore, that there is little evidence of severe renal damage while the albuminuria accompanying the edema of typical nephrosis is not found.

Essen and Porges [20] suggested that a deficiency of oxygen in the blood, dependent on the anemia, is responsible for the faulty functioning of the renal tissues. Meulengracht [17] and Kofanov,[18] however, showed that there is no disturbance of the excretion of water in either posthemorrhagic or chlorotic types of anemia, so that it is unlikely that the anemia itself, through its effect on the kidney, is responsible.

The questions of changes in the plasma proteins and colloidal osmotic pressure in the plasma have recently received attention. De Wesselow [21] studied nine patients who were receiving liver therapy and found, as earlier observers, Kahn and Barsky,[22] and Gettler and Lindeman [19] had done, that in severe stages of anemia there is a slight lowering of total plasma protein with a return to normal in the remission. He did not, however, consider the changes to be of significance. Meulengracht [17] made comparative observations on the colloidal osmotic pressure in the plasma in nephrosis, in pernicious anemia and in secondary anemia. He found that although in some patients with pernicious anemia the pressure was lowered as much as that in the nephrotic patients, this reduction was dependent on quantitative rather than on qualitative changes. Furthermore, some cases of posthemorrhagic anemia had a similar lowering of colloidal osmotic pressure with no edema. There also

19. Gettler, A. O., and Lindeman, E.: The Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26**:453 (Oct.) 1920.

20. Essen, H., and Porges, O.: Ueber der Nierenfunktion bei Anämien, Wien. Arch. f. inn. Med. **5**:195, 1923.

21. deWesselow, O. L. V., and Barnforth, J.: The Blood and Plasma Volume in Pernicious Anemia, Lancet **1**:1066 (May 26) 1930.

22. Kahn, M., and Barsky, J.: Studies of the Chemistry of Pernicious Anemia, Arch. Int. Med. **23**:334 (March) 1919.

appeared to be no constant parallelism between the amount of edema and the reduction in the excretion of fluids on the one hand and the lowering of colloidal osmotic pressure on the other. Though the lowering of plasma proteins may be a contributory cause of the edema present in pernicious anemia, it cannot alone be responsible.

It is possible that changes in the general metabolism of the body may be, in part at least, responsible for this retention of water. Newburgh [23] recently showed that pronounced changes in the balance between weight and water may be caused by varying the carbohydrate content of a diet in which the caloric value is kept constant, and also that considerable destruction of body tissues may be marked by the retention of water. It is known that certain profound changes do occur in the chemical constituents of the blood at the time of a remission. Muller [24] found that there is a rise in plasma cholesterol at this period, and Riddle [25] reported an increase in the uric acid, which rises and then falls, having the same relationship to the reticulocyte peak as does the intake of fluids. It is clear that careful and elaborate studies along the lines suggested by Newburgh [26] of a series of patients with pernicious anemia at the time of remission are required to enable one to determine the nature of the essential factors underlying the disturbance of the balance of water occurring at this time.

BASAL METABOLIC RATE

Observations on the basal metabolic rate in the present series of cases were not complete, but they agree with those of the majority of other observers in demonstrating that the improvement in the blood picture is associated with a return of the basal metabolic rate to normal or subnormal levels. Before the introduction of liver therapy, Meyer and DuBois,[27] Magnus-Levy,[28] Boothby and Sandiford,[29] and Becker [30]

23. Newburgh, L. H., and Johnston, M. W.: The Nature of Obesity, J. Clin. Investigation **8**:215 (Feb.) 1930.

24. Muller, G. L.: The Relations of Cholesterol, Lecithin, Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, Am. J. M. Sc. **179**:316 (March) 1930.

25. Riddle, M. C.: The Endogenous Uric Acid Metabolism in Pernicious Anemia, J. Clin. Investigation **8**:69 (Dec.) 1929.

26. Newburgh, L. H.; Johnston, M. W., and Falcon-Lesses, M.: Measurement of Total Water Exchange, J. Clin. Investigation **8**:197 (Feb.) 1930.

27. Meyer, A. L., and DuBois, E. B.: Clinical Calorimetry, XV; The Basal Metabolism in Pernicious Anemia, Arch. Int. Med. **17**:965 (June) 1916.

28. Magnus-Levy, A.: Der Einfluss von Krankheiten auf den Energieaushalt im Ruhezustand, Ztschr. f. klin. Med. **60**:177, 1906.

29. Boothby, W. B., and Sandiford, I.: Summary of the Basal Metabolism Data on 8,614 Subjects with Special Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, J. Biol. Chem. **54**:783 (Dec.) 1922.

30. Becker, G.: Studien über den Stoffwechsel bei perniziöser Anämie, Acta med. Scandinav. **63**:478, 1925-1926.

reported a definite increase in metabolic rate during relapses, which returned to normal limits in the remissions. Tompkins, Brittingham and Drinker [31] discussed a series of cases in which the level of the basal metabolic rate was either above or below normal during relapse, but in which during remissions, induced by transfusion, it returned to normal. Grassheim [32] alone did not agree with this observation. Richards and Straus,[33] Alt,[34] and Bauer and Baldridge [35] made the same observations in cases in which the patients received either liver or liver extract. Alt claimed that the reticulocyte peak is accompanied by a rise in metabolic rate, but his figures are not convincing and are in disagreement with the extremely careful daily observations of Bauer and Baldridge. Three observations made on the cases in the present series at the time of the reticulocyte response showed no increase in metabolic rate.

SUMMARY

Correlation of the previous observations would seem to show that changes of the basal metabolic rate such as are found in myxedema are in no way responsible for the gain in weight occurring during a remission in pernicious anemia. Two factors would appear to be involved: (1) an initial retention of water and subsequent edema, which is transitory, the increase in weight at this period being due to increase in water, and (2) an increased caloric intake associated with the general improvement of the patient, the increase in weight now being due to increase in the body tissues.

None of the patients in the present series showed the startling gain in weight that has been reported in some instances. It is clear, therefore, that more prolonged and detailed observations are required before it is possible to determine whether or not the increased caloric intake alone is always sufficient to account for the increase in body weight. As far as the evidence can be judged at present it would appear, however, that caloric intake plays at least an important rôle.

31. Tompkins, E. A.; Brittingham, H. H., and Drinker, C. K.: The Basal Metabolism in Anemia with Special Reference to the Effects of Blood Transfusion on the Metabolism in Pernicious Anemia, Arch. Int. Med. **23**:441 (April) 1919.

32. Grassheim, K.: Stoffwechseluntersuchungen bei perniziöser Anämie, Ztschr. f. klin. Med. **111**:601, 1929.

33. Richards, D. W., and Straus, M. L.: Circulatory Adjustment in Anemia, J. Clin. Investigation **5**:161 (Feb.) 1928.

34. Alt, H. L.: The Metabolism in Pernicious Anemia, Arch. Int. Med **43**: 488 (April) 1929.

35. Bauer, A., and Baldridge, C. W.: The Effect of Liver Extract on the Basal Metabolic Rate in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **26**:872 (June) 1929.

CONCLUSIONS

1. Observations on the relation of gain in weight to caloric intake, fluid balance, basal metabolism and improvement in the red blood cell count have been made on twelve patients with pernicious anemia.

2. Eleven patients showed an initial gain in weight irrespective of diet at the height of the reticulocyte rise, associated with retention of fluid and the appearance of gross edema.

3. This initial gain in weight was followed by increased excretion of urine, disappearance or diminution of edema and loss of weight.

4. A body weight exceeding that at the onset of treatment, with one exception, was found only in the patients receiving an ample diet.

5. The improvement in the red cell count was associated with a return of the basal metabolic rate to normal or subnormal levels.

6. The initial gain in weight associated with a remission in pernicious anemia would appear to be dependent on the retention of fluids, while increased caloric intake is, at least in part, responsible for the more prolonged gain in weight.

THE AVERAGE DAILY ELIMINATION OF UROBILINOGEN IN HEALTH AND IN DISEASE, WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA

STANDARDIZATION OF METHOD BASED ON MESOBILIRUBINOGEN (H. FISCHER)*

C. J. WATSON, M.D.
MINNEAPOLIS

Relatively little use is made in clinical investigation of the considerable existing knowledge concerning the circulation and elimination of urobilinogen. This is not because of any general doubt about the significance of urobilin in the urine and feces, because the relationship of its concentration in these excreta to hepatic function, obstruction of the bile passages and destruction of the blood has been demonstrated repeatedly. Rather, the apathy in this regard may be attributed to the lack of any generally accepted method of quantitation and of exact knowledge concerning the daily output in health and disease. This report is the culmination of work begun three years ago, the purpose of which was to survey methods of estimation previously described in the literature and to use a method found to be reasonably accurate in ascertaining the average amount of urobilin eliminated per day in both normal and sick persons.

HISTORICAL REVIEW

Since the original description of urobilin by Jaffe, in 1868, an extensive literature has accumulated. The earlier publications were discussed in a review by Meyer-Betz in 1913. Wilbur and Addis, in 1914, with the description of their quantitative procedure, included a complete review of previously described methods. A fairly thorough critical discussion of the literature to 1920 may be found in Eppinger's book "Die Hepato-Lienalen Erkrankungen." These publications make unnecessary any exhaustive discussion of the literature, and in the following paragraphs only the more salient contributions will be considered. Following Jaffe's discovery of urobilin in the urine and bile, a similar pigment was observed in feces by Van Lair and Masius. Maly's hydrobilirubin, obtained by reduction of bilirubin, while later shown to be not identical with urobilinogen, nevertheless gave strong impetus to the enterogenous theory of formation of the urobilin, which

* Submitted for publication, Sept. 11, 1930.

* From the Northwest Clinic, Minot, N. D., and the Minneapolis General Hospital.

was firmly supported by the clinical and experimental investigation of Muelier. (This, in particular, consisted of the feeding of urobilin-free pig bile to a person with obstruction of the common duct whose stools and urine contained no urobilin, with its subsequent appearance in both). Le Nobel, in 1887, had given the name urobilinogen to the leuko-compound obtained by the reduction of bilirubin or urobilin. Saillet, ten years later, studied this chromogen intensively, and noted the ease with which it could be oxidized and that it was particularly sensitive to light. In 1903, Neubauer pointed out that the hitherto mysterious aldehyde reaction of Ehrlich, commonly occurring in pathologic urines, was due to the presence of urobilinogen. This reaction was employed by Charnas in a spectrophotometric method for the examination of urine and later of feces, and while criticism of this method in later years by Wilbur and Addis and Terwen is undoubtedly made with reason, the results obtained by its use, as published by Eppinger and Charnas, amply illustrate the value of such a procedure in clinical investigation. In 1911-1914, Hans Fischer and his associates afforded the most exact information yet obtained on the subject of chemical examination of urobilin. Stated as briefly as possible, this admirable work accomplished the following: (*a*) isolation of crystalline "hemibilirubin" following the reduction of bilirubin by sodium amalgam (so-called because yield was approximately 50 per cent); (*b*) isolation of crystalline urobilinogen from urine and crystallographic proof that hemibilirubin and urobilinogen are identical; (*c*) conclusive evidence. that the previously described urobilins of Maly, and of Garrod and Hopkins, were mixtures, and that the hemopyrrol of Nencki and Zaleski is not the same as urinary urobilinogen.

As a result of this work, urobilinogen emerged as a definite substance while urobilin as yet has no identity. While urobilin is usually considered the oxidation product of urobilinogen, a chemical individual with urobilin characteristics has not been isolated by treatment of native urobilinogen or in vitro reduction products of bilirubin. On the contrary, Fischer was later able to show that the crystalline product in close relation with bilirubin, obtained by reduction of the latter, to which he gave the name mesobilirubin, was also in close relationship with hemibilirubin, or urobilinogen. This substance, however, failed to give the zinc fluorescence characteristic of urobilin. Fischer was induced to change the name of hemibilirubin to mesobilirubinogen because of its evident relationship to mesobilirubin and bilirubin. He was inclined to believe that what is ordinarily called urobilin is urobilinogen in relation with bile acids or cholesterol. Stercobilin was definitely shown to be a mixture. Because of the half yield in the reduction of bilirubin and because at first, all of the aldehyde reacting substance could not be removed from the urine with the one

procedure used, it was not possible to be sure that only one urobilinogen existed. A later method removed the substance quantitatively and, since it is identical with mesobilirubinogen, Fischer considered it to be probably the only urobilinogen. The constitution is that of a dibasic acid with four pyrrol nuclei (empirical formula, $C_{33}H_{44}N_4O_6$) and with one methin group, the latter responsible for the Ehrlich reaction.

Writers of articles on clinical medicine have given surprisingly little attention to these important observations in the description and discussion of methods. Eppinger considered it unfortunate that Fischer did not attempt the isolation of crystalline urobilinogen by application of his methods to feces directly rather than by the study of "stercobilin." Charnas, in 1913, described the isolation of crystalline urobilinogen from feces. This substance was found to differ in some respects from hemibilirubin: detailed characteristics and analyses were not given.

Eppinger's review, in 1920, contained a full discussion of the origin of urobilin and summed up the considerable evidence in favor of the enterogenous theory. In 1923, this sum total was increased by the work of Kämmerer and Miller, who were able to produce urobilin in vitro by allowing bilirubin to remain in contact with feces under anaerobic conditions. Two years later the series of publications by Elman and McMaster, who employed the new technic of Rous and McMaster for sterile biliary fistula, offered convincing evidence of the enterogenous origin of urobilin in dogs. These investigators also demonstrated experimentally the enterohepatic circulation of urobilin and the consequent importance of urobilinuria in the study of the function of the liver. (Eppinger, from clinical observation of the duodenal contents, arrived at the belief that urobilin was rarely present in the normal bile and that the portion resorbed from the bowel must, under normal conditions, be entirely utilized by the liver, albeit in an unknown way.)

In the experiments of Elman and McMaster, urobilin promptly appeared in the urine with obstruction of the bile ducts to as little as one third of the parenchyma of the liver. The recent clinical observations of Wallace and Diamond are not in accord with this observation; with their method the amount of urobilin in the urine was not increased in extrahepatic obstruction of the bile duct, but was characteristic of injury to the parenchyma of the liver. In a recent study of tests for liver function, Piersol and Rothman stated the opinion that urobilinuria is the most delicate single evidence of derangement of the liver. Elman and McMaster also obtained evidence to show that urobilin may be formed in infected biliary passages with complete obstruction of the common duct. The urobilinuria, which occurred with increased destruction of the blood produced experimentally, was considered evidence of a simple excess in amount over that which the liver could excrete into

the bile. This was not Fischer's opinion, since he found only a moderate amount of urine aldehyde reactions not comparable with those often seen in pathologic urines after feeding hemibilirubin to normal persons.

Methods of quantitative estimation reported in the literature are numerous. A complete review of these is found in the publication by Wilbur and Addis, in 1914, and again in Eppinger's "Die Hepato-Lienalen Erkrankungen," in 1920. Apart from the gravimetric method described by Hoppe-Seyler, the various methods have utilized either the fluorescence of urobilin with zinc salts or the urobilinogen aldehyde reaction or both, and these have been employed in colorimetric or dilution methods (the latter, either of color or absorption bands). The spectrophotometric method may be placed in the latter group. This was first used by Gerhardt and Mueller, who accepted Vierordt's absorption value for Maly's hydrobilirubin. Charnas was the first to employ the aldehyde reaction in a quantitative method; he also used the spectrophotometer. His standard substance was obtained by the technic of Garrod and Hopkins. As mentioned previously, this as well as the hydrobilirubin of Maly were shown by Fischer not to be chemical individuals. Apart from this objection, two other features of Charnas' method have received unfavorable criticism. In the method as applied to urines, a period of alkaline fermentation was allowed during which it was believed that any urobilin present was converted to urobilinogen. In the experience of Wilbur and Addis, the opposite is true. This feature was also criticized by Meyer-Betz and Terwen. As regards Charnas' method for feces, Terwen has pointed out that loss of urobilinogen occurs when the alkaline extract is washed with ether. Soon after the publication of the latter method by Eppinger and Charnas, in 1913, Brugsch and Retzlaff employed a modification of it to standardize a colorimetric method. The values obtained with this method, so far as they can be compared, and also with a later modification of Charnas' method as described by Hueck and Brehme, in 1923, are lower than those of Eppinger and Charnas.

Methods based on fluorescence alone, whether colorimetric or dilution, are subject to two criticisms in general regardless of the individual procedures. The fluorescence with zinc salts varies considerably with conditions present in the solution, and while these may be adjusted according to Marcussen and Hanson, no method employing fluorescence has been based on a crystalline substance, with the exception of that recently described by Opitz and Choremis in which Fischer's mesobilirubinogen was used to standardize a modification of Adler's earlier technic. Adler has pointed out the extreme range of strength of fluorescence of the urobilins of various writers, hemibilirubin or mesobilirubinogen, after oxidation, having a much more intense fluorescence than any of the other materials. In addition to this, the lack of chemical

individuality of urobilin, together with Fischer's belief that what is commonly designated as urobilin in the urine is probably urobilinogen in some relation with a fluorescent derivative of a bile acid or cholesterol, casts doubt on the usefulness of fluorescence and will continue to do so until (according to Fischer) there are reported more exact quantitative analyses of urobilin-containing urines as to urobilinogen, bile acids and cholesterol. Adler has recently abandoned his method based on fluorescence in favor of a new extraction apparatus for quantitation of mesobilirubinogen. The method used by Elman and McMaster in their experimental work was a colorimetric procedure in which fluorescence was compared with standard acriflavine solution, the latter originally standardized with urobilin isolated by a modification of Garrod and Hopkins' technic. This method of quantitation has recently been employed by Royer in a variety of clinical investigations and by Edelman, Halpern and Killian in demonstrating the prognostic value of urobilinuria in cardiac failure.

Methods depending on dilution of absorption bands have been considerably used, more particularly in the United States, where the technic described by Wilbur and Addis, in 1914, has been popular. These investigators did not believe it possible to standardize any method on a chemical individual (although their publication was subsequent to that of Fischer's work on urobilinogen). In this method, the absorption bands of the zinc compound of urobilin and the urobilinogen-aldehyde dye are diluted out one at a time in the same solution of urine or stool; the sum of the two dilutions is the value reported. Dilution values for either absorption bands or fluorescence are subject to the personal equation in marked degree. Another objection to this method has recently been pointed out by Terwen, i. e., that since indol and skatol produce the same color and absorption band as does the urobilinogen-aldehyde compound (550-570), it is obviously necessary to remove these substances and this was not taken into account by Wilbur and Addis. Saillet and Simpson had previously used spectroscopic dilution procedures based on the urobilin band alone.

Charnas, as mentioned previously was the first to apply the aldehyde reaction to a quantitative method. Some loss of urobilin undoubtedly occurred by this method as well as by that of Brugsch and Retzlaff, in the attempt to remove the interfering indol-skatol. The dilution methods of Flatow and Brünell and of Wallace and Diamond neglect these substances. With the doubtful exception of Charnas' fermentation transformation of urobilin to urobilinogen, all of these methods attempted to measure only the preformed urobilinogen. In 1925, an admirable method was described by Terwen in which urobilinogen, both preformed and oxidized, is estimated as one, and indol-skatol definitely eliminated. Here again the question of chemical identity of urobilin

arises: it is definite that urobilinogen develops increasing fluorescence on exposure to air and light and becomes darker, while the urobilin absorption band appears in such an exposed solution. Terwen was able to show that the Ehrlich reaction increased, and that the urobilin band diminishes or disappears with reduction of the type used in his method. In 1927, an apparatus for the quantitative extraction of mesobilirubinogen was reported by Adler, and a year later (1928) clinical results with this method were published by Adler and Bressel. Terwen's method was standardized on a noncrystalline urobilin, while Adler's procedure estimates only the preformed urobilinogen.

DESCRIPTION OF METHOD

Of the foregoing methods, that described by Terwen was believed superior for clinical application. While Adler's technic quantitates a chemical individual, the apparatus is too complicated for the average clinical laboratory, and although the method is said to be colorimetric, no details of the colorimetric procedure are given. Terwen's method was applied to both urine and feces; reduction and alkaline extraction are carried out simultaneously by a ferrous hydroxide precipitate with an excess of sodium hydroxide. The clear filtrate should not contain any urobilin band; it is acidified with strong tartaric acid and the urobilinogen extracted with ether. Paradimethylaminobenzaldehyde in ether is added to a portion of this in another separatory funnel followed by concentrated hydrochloric acid, a little distilled water and a small amount of a saturated solution of sodium acetate. The latter is important, since Terwen was able to show that the red color formed by indol and the aldehyde is stable only in the presence of a mineral acid, while the urobilinogen-aldehyde color is unaffected by the formation of acetic acid. The acetic acid is also less likely to promote oxidation of the urobilinogen. Precipitation of any excess aldehyde in the lower aqueous fraction is effected, so that the yellow color returns to the ether. All of these changes are undoubtedly attributable simply to a decrease in the hydrogen ion concentration of the aqueous portion. More than one extraction is necessary if considerable urobilinogen is present. The final colored solution is compared in an Autenrieth colorimeter with a standard sodium carbonate-phenolphthalein solution. This method was modified in the following ways, and was standardized with crystalline hemibilirubin or mesobilirubinogen (urobilinogen), as discussed later:

1. A greater dilution was used in the primary extraction. Ferrous sulphate was used rather than ferrous ammonium sulphate as in Terwen's method, with relatively more of the ferrous salt and relatively less sodium hydroxide. This makes both the extraction and reduction more efficient.

2. The period of reduction was shortened to one hour. Terwen indicated that reduction was complete within a relatively short time, but stipulated that the original flask should be set aside over night. In my experience, the filtrate usually presents no urobilin absorption band after one hour, while one is not infrequently present when left over night. Furthermore, repeated colorimetric comparisons at intervals indicated that the optimum reduction is reached within from forty-five to ninety minutes.

3. Suction flasks were used for the primary extraction and reduction with evacuation to hinder reoxidation.

4. Occasional supplementary reduction in the filtrate was obtained with small amounts of sodium amalgam. The presence of a definite urobilin band in the filtrate requires further reduction, and this is more easily accomplished by adding a small amount of 5 per cent sodium amalgam to 10 or 15 cc. of filtrate for a short period than to recommence with larger amounts of the ferrous salt and sodium hydroxide. Adler suggested that reduction, as in Terwen's method, might produce some undesirable effect on the urobilinogen. Terwen's control experiments did not indicate the existence of any such effect, and I did not find any significant variation in color before and after sodium amalgam had been in contact for a short time with a filtrate in which ferrous hydroxide reduction had just previously taken place.

5. The amount of filtrate used was varied to correspond to the relative amount of urobilinogen present, thus making the method more sensitive and the color comparisons more uniform, as well as reducing the number of extractions to a minimum. Terwen used a fixed amount of filtrate, 2 cc. in analyses of the stools and 20 cc. in the case of urine. Fürth and Singer recently pointed out the advantage of using large amounts of filtrate in estimating minute quantities of urobilinogen in the stool, as when an incomplete obstructive jaundice exists.

6. The method of using the entire ether extract was simplified so that only one separatory funnel is necessary, without any transference of solutions. Terwen's use of an aliquot of the ether extract is assumed to be due to the slight solubility of ether in water or to retain in reserve some of the ether extract in case a check was believed necessary; however, even when the original filtrate is rich in urobilinogen, after one ether extraction the aqueous fraction fails to give any aldehyde reaction. If a check is considered advisable, it is more satisfactory to begin with fresh unexposed filtrate. Emulsions are uncommon and do not give rise to difficulty.

7. Acetic rather than tartaric acid was used for acidification of the alkaline filtrate. This is more convenient and does not produce any error. Comparative estimations on the same filtrate failed to show any loss when acetic acid was employed. This was also the experience of Fürth and Singer. Terwen presumably used tartaric acid because of its insolubility in ether. In the present method, the urobilinogen remains in the ether for only a short period; in any event, some acetic acid is present in the end-solution.

With these modifications, the method of analyses of the feces and urine is subsequently given. The manner in which stools are collected, weighed and mixed prior to the estimation is described in detail. It is believed of greatest importance to obtain the average value for several days. This is also the opinion of Adler and of Opitz and Choremis. It is obvious that with many persons estimation of the fecal urobilinogen for twenty-four hours is of little value because of the considerable variation in the amounts of stool. Wilbur and Addis observed marked fluctuations of urobilin in the urine from day to day. The following method estimates preformed urobilinogen and urobilinogen which has been changed to the substance ordinarily known as "urobilin."

Collection of Feces.—If the patient is having regular defecation of formed stools daily at relatively the same time, it is sufficient to save all stools for four days, counting from an hour at which one was discarded. The last stool is collected at relatively the same hour four days later. Specimens for the first and second forty-eight hours are collected separately and analyzed separately at the end of two and four day intervals. In this way the output of urobilinogen may be followed over some period by the daily average for consecutive two day periods, or the daily average for a single four day period may suffice. Specimens are

most conveniently kept in the ordinary cylindric waxed cardboard cartons of liter capacity. These will usually contain all of the forty-eight hour stool, unless enemas have been necessary. They should be kept in a cool place, with exclusion of light, during the period prior to analysis.

Satisfactory collection for analysis is much more difficult in persons who are not having regular defecation. In spastic constipation, it is advisable to defer the period of collection for a few days until antispasmodics and nonirritating roughage have brought about normal bowel movements. In atonic conditions, cascara in moderate doses is believed advisable. Mineral oil by mouth or oil enemas are not advisable. Whenever the patient to be studied does not have regular stools at approximately the same time daily, it is best to begin the period of collection with a water enema (from ½ to 1 pint) the results of which are discarded; exactly four days later, another enema is given the results of which are included with the last forty-eight hour collection. If the amount of stool during the four day period is very small and fecal impaction is found on rectal examination, this should be broken up with the gloved finger and a water enema of 1 pint administered, the results of which are included in the collection. It is often difficult to study the excretion of urobilin in the stool in persons who are critically ill, both because they do not eat a sufficient amount to create residue and because of the atonic condition of the bowels. A certain amount of residue is undoubtedly necessary to promote excretion at a normal rate, since, as Wilbur and Addis have observed, the output of urobilinogen is diminished in constipation, presumably because of the greater time allowed for resorption. It is probable that values will be too low unless the total amount of stool examined for the four day period is at least from 250 to 300 Gm., depending on the size of the person. This is, of course, exclusive of enema fluid. The collection of stools during a period of diarrhea is not advisable since the rapid passage of intestinal contents fails to permit normal resorption. In reporting estimations of the daily output of urobilin, it is advisable to mention the amount of the four day stool specimen.

Measurement and Mixture of Stool Specimens.—The entire forty-eight hour specimen must be weighed prior to analysis. An empty container of the same size as that containing the specimen is placed on the balance pan opposite the specimen. In this way the stool may be weighed directly. The forty-eight hour stool specimen must be mixed so that all parts are relatively equal. In the case of stools having at least a moderate degree of consistency, mixture may be made in the collection container directly. The iron rod of a ring stand is useful for this purpose, as it is easily cleaned. Stools that are liquid or partly so must be thoroughly homogeneized in a large mortar. If the specimen is partly solid and partly liquid, mixture is best accomplished by first pouring the liquid portion into a beaker, transferring the solid portion to the mortar where it is ground up with the pestle, and then adding the liquid from time to time until all is thoroughly mixed.

Method of Quantitation.—The following materials are required: 1 liter mortar and pestle; one small mortar and pestle; one 250 cc. evaporating dish; one suction flask of 250 cc. capacity equipped with a 12 inch length of heavy walled rubber tubing fitted on the suction arm; a few plain stiff clamps or hemostatic forceps (strong pinchcocks may be used); several 5 cc. pipets graduated in 1 cc., and 1 cc. pipets graduated in 0.1 cc.; a spectroscope (small hand size is sufficient); a Van Slyke type of separatory funnel capable of holding 250 cc.; a few ordinary 15 to 20 cc. test tubes and a few 50 or 100 cc. graduated test tubes or cylinders, and a colorimeter, preferably of the DuBoscq type, although any reasonably accurate colorimeter may be used. In the present series of estimations, a Klett biocolori-

meter was employed. If more than one determination is to be made, it will be necessary to have two or three of the suction flasks.

The following reagents are required: Ehrlich's reagent, composed of 10 Gm. of paradimethylaminobenzaldehyde, 75 cc. of concentrated hydrochloric acid and 75 cc. of distilled water; crystalline ferrous sulphate ($FeSo_4$ 12 H_2O); 10 per cent sodium hydroxide; 5 per cent sodium amalgam; 20 per cent acetic acid; pure ether (diethyl); saturated ethereal solution of para dimethylaminobenzaldehyde (should be light yellow, as definite redness or darkness indicates impurity); concentrated hydrochloric acid in a dropping bottle; a saturated solution of sodium acetate (aqueous); a saturated solution of sodium carbonate (aqueous); 0.05 per cent alcoholic solution of phenolphthalein (50 mg. of pure phenolphthalein in 100 cc. of 95 per cent alcohol kept in a glass stoppered bottle will suffice for a large number of determinations).

Procedure for Analysis.—Weigh out 5 Gm. of the mixed stool on filter paper, or if not sufficiently dry, in an evaporating dish. Transfer to a small mortar. The ordinary cheap wooden tongue depressor is very useful in weighing and transferring. Add a small amount of water from a measured portion of 95 cc. Grind thoroughly with a pestle; it is important that the particles of feces be finely ground. Adler has observed that small fecal particles adsorb urobilin and hinder extraction. Add the remainder of the water and again mix completely. Let this mixture stand a moment or two while measuring out 50 cc. of 10 per cent sodium hydroxide. Decant the supernatant portion from the mortar into a small flask (Florence, preferably). Again grind up the remaining precipitate and fluid, then add the 50 cc. of sodium hydroxide and add all of this to the first portion in the flask. Shake vigorously for a few moments. Pulverize 10 Gm. of ferrous sulphate on the filter paper on which it was weighed and place in the 250 cc. suction flask, the side arm of which is fitted with heavy walled rubber tubing. Add 46 cc. of distilled water and shake until the majority has gone into solution. Now add to this in small portions and with vigorous shaking all of the fecal emulsion from the other flask. Cork tightly and evacuate with suction. When vacuum is considerable, clamp the rubber tube with forcep or stiff clamp. Set aside in the dark for one hour. At the end of this period, filter from 3 to 4 cc. into an ordinary test tube. Examine this with a hand spectroscope for the presence of a definite absorption band of alkaline urobilin (495-515). Rarely more than a faint urobilin band is seen, and in this event further reduction is necessary. To approximately 15 cc. of the filtrate in a 50 cc. graduated centrifuge tube, add from 1 to 2 Gm. of 5 per cent sodium amalgam. Cork lightly and set aside in the dark for ten minutes. A second period of ten minutes may be necessary for disappearance of the urobilin band. If sodium amalgam is not at hand, the following method may be substituted: weigh out another 5 Gm. of the mixed stool specimen and proceed exactly as before, except use double the amount of both the 20 per cent ferrous sulphate and the 10 per cent sodium hydroxide (100 cc.); this makes the value of the primary dilution 60, while it is ordinarily 40.

To a few cubic centimeters of the urobilin-free filtrate (as examined spectroscopically) in a test tube, add Ehrlich's reagent from a dropping bottle, drop by drop, until cloudiness has disappeared. The amount of red which develops immediately determines roughly how much filtrate is to be used in the quantitative determination. The following is a useful, but not necessarily absolute, list of the degrees of color and corresponding amounts of filtrate to be used: (1) deep red with a slight bluish tinge, 1 cc.; (2) light red, 2 cc.; (3) pink, 5 cc.; (4) barely discernible pink, 10 cc.; (5) no color and absent urobilinogen—aldehyde absorption band—(550-570), from 25 to 50 cc. (If a new specimen, 50 cc. should be

employed, but if color has recently been present in previous specimens, 25 cc. is probably enough.)

In a series of determinations made every other day on specimens from the same patient, after the first day it is usually sufficient to use the same amount of filtrate each time.

Place the amount of filtrate chosen in a separatory funnel and acidify with an excess of 20 per cent acetic acid (0.4 cc. per cubic centimeter of filtrate constitutes a definite excess). At once add approximately 40 cc. of pure ether (diethyl). The amount need not be exactly measured. Shake vigorously for from two to three minutes. (When larger amounts of filtrates are used, the shaking must be relatively more gentle; from 75 to 100 inversions will suffice). Allow the aqueous fraction to separate, then drain it off and discard. Wash the ether once with a small portion of distilled water, and discard the latter. From a 5 cc. pipet add 3 cc. of a saturated ethereal solution of paradimethylaminobenzaldehyde. Add 10 drops of concentrated hydrochloric acid from a dropping bottle. Shake vigorously for from one to two minutes. Add a few cubic centimeters of distilled water and shake briefly. Add 3 cc. of a saturated aqueous solution of sodium acetate and again shake. Separate off the colored solution into a 50 cc. graduated centrifuge tube or cylinder. Place this in a glass or rack and cover temporarily with a cloth or towel. Repeat the following extraction, using only 5 drops of hydrochloric acid, a smaller amount of water and 2 cc. of the sodium acetate solution. More of the aldehyde need not be added. If not too much filtrate is chosen in the first instance, three such extractions will suffice. Sometimes, when the amount of urobilinogen is large, four or five extractions will be necessary. The last extraction should yield only a faint color. When all of the colored aqueous portions have been collected in the same graduated tube, this collection is made up to a volume which is a multiple of the original amount of filtrate taken. If the color is pale, dilution should be only to the next cubic centimeter. This solution is thoroughly mixed, and a portion of it is placed in one colorimeter cup. Some of the standard phenolphthalein solution is placed in the other cup. This is composed as follows (according to Terwen): 1 cc. of 0.05 per cent alcoholic solution of phenolphthalein, and 5 cc. of saturated aqueous solution of sodium carbonate. Make up to volume with distilled water in 100 cc. volumetric flask. Prepare fresh the same day.

As subsequently shown in detail, this standard solution has a color equivalent so that of 0.4 mg. of urobilinogen condensed with paradimethylaminobenzaldehyde and hydrochloric acid in 100 cc. Calculations are then as follows: D_1 (usually 40) $\times$ $D_2 = \frac{\text{Volume of final solution}}{\text{Volume of filtrate used}} \times \frac{S}{R} \times 0.4 =$ mg. of urobilinogen in 100 Gm. of stool. Multiply this by the weight of the entire stool specimen and divide by 100 to obtain the total amount of urobilinogen. At the end of the period of collection (usually four days), the amounts obtained are added together and the sum divided by the number of days. This final result is the average daily output in milligrams.

The foregoing extraction procedure should be carried out in subdued light, preferably artificial.

It is essential that no alkali should come in contact with the final colored solution, as the dyestuff is decomposed by alkali, with complete loss of the red color (Fischer).

Collection of Urine.—Urine is collected for two forty-eight hour periods in gallon bottles in which have been placed from 20 to 30 cc. of a saturated alcoholic solution of salicylic acid, for preservation. (The salicylic acid has been shown

by Terwen not to have any effect on the subsequent estimation.) During collection, these bottles should be kept in a cool, dark place.

The forty-eight hour urine should be mixed and measured. If deeply colored, or if bilirubinuria is suspected, bilirubin should be tested for, the Gmelin, Huppert-Cole or van den Bergh test being used. If bilirubin is found to be present in more than traces, preliminary treatment is necessary to eliminate it, as with the foregoing method a certain amount of color may be produced by the reduction of bilirubin alone, in the absence of urobilinogen. (Pure bilirubin was dissolved in 10 per cent sodium hydroxide; this was added to 20 per cent ferrous sulphate as in the foregoing procedure, and after standing in the dark one hour the filtrate was found to give a definite aldehyde reaction with the same extraction technic used for the stool filtrate. Terwen apparently did not consider that the bilirubin was reduced in any degree, as he advises the use of petroleum ether in place of ether which, he states, does not extract bilirubin from the acidified filtrate.)

To free the urine of bilirubin, add to 200 cc. of urine 100 cc. of a saturated aqueous solution of calcium hydroxide with slight excess not in solution, and to which has been added a relatively small amount of 10 per cent sodium hydroxide. Shake these solutions together in a beaker and let stand for a short time. The bilirubin is precipitated as insoluble calcium bilirubinate. Then filter. The filtrate is used in place of bilirubin-free urine in other determinations and the added dilution of 1.5 is taken into account in the final calculation.

To 5 Gm. of ferrous sulphate in the suction flask with rubber tubing on the suction arm, add 23 cc. of distilled water. To this add 100 cc. of the mixed bilirubin-free urine, or filtrate to be tested. Then add in small portions at a time and with constant shaking 25 cc. 10 per cent sodium hydroxide. Evacuate, clamp and set aside in dark for one hour. The procedure from now on is the same as in the case of the determination on the stool, except that it is necessary to use larger amounts of filtrate, especially with normal urines and bilirubin filtrates of urines containing small amounts of urobilin. Fifty cubic centimeters of filtrate should be employed in such instances.

Normally, there is rarely more than a trace of urobilin present in the urine, and the amount of color obtained from 50 cc. of filtrate is often so small that accurate comparison of the color is impossible. It is better in such an instance to report simply a trace, rather than a figure which is not liable to be accurate. In the present series more than 50 cc. of filtrate have not been used.

When urine alone is used, the method of calculation is as follows:

$$D_1\ (1.5) \times D_2 \left(\frac{\text{Final volume}}{\text{Amount of filtrate}}\right) \times \frac{S}{R} \times 0.4$$

This multiplied by the number of cubic centimeters of urine in the entire specimen and divided by 100 gives the total number of milligrams present.

When calcium hydroxide has been used to precipitate bilirubin, the calculation is done as follows:

$$D_1\ (1.5) \times D\ (1.5) \times D_2 \left(\frac{\text{Final volume}}{\text{Amount of filtrate}}\right) \times \frac{S}{R} \times 0.4$$

STANDARDIZATION OF METHOD AND DATA RELATIVE TO THE OTHER MODIFICATIONS

1. Strength of the standard phenolphthalein solution in terms of milligrams urobilinogen per hundred cubic centimeters. Since no figure was found in the literature representing the equivalent of a definite amount of crystalline urobilin-

ogen condensed with Ehrlich's reagent, with a standard color solution, the following experiments were undertaken:

(*a*) Hemibilirubin or mesobilirubinogen was prepared in small quantity according to the procedure described by Fischer, with decrease in all amounts corresponding to decrease in bilirubin. (The latter is very expensive whether purchased pure or obtained from gallstones of cattle.) Bilirubin (Eastman), 200 mg., was dissolved in 3 cc. of tenth-normal sodium hydroxide, to which was added 1.5 cc. of water. This was reduced over night in a 10 cc. Erlenmeyer flask with approximately 5 Gm. of 4.6 per cent sodium amalgam. The light brown solution was acidified with 50 per cent sulphuric acid and shaken out four times with 4 cc.

Mesobilirubinogen crystals.

amounts of chloroform. The latter was dried superficially over anhydrous sodium sulphate, after being filtered. It was then concentrated in partial vacuum in an atmosphere of carbon dioxide and protected from the light. The remaining syrup was taken up in about 4 cc. of ethyl acetate, 3 cc. of petroleum ether added, filtered and again concentrated in the same way, then again taken up in hot acetic ester (from 4 to 5 cc.), to which a little petroleum ether was added, filtered and cooled. A small separation of apparently colorless, very small crystals took place. These were filtered off and the mother liquor concentrated to a small volume, so that the yield was increased to approximately 20 mg. It was placed at once in a vacuum desiccator over P_2O_5. A few of the crystals were examined

and found to be apparently identical with those of hemibilirubin described by Fischer. No measurements were made. The hemibilirubin crystals as observed are shown in the sketch. While the substance was apparently colorless on first crystallization, it quickly assumed a light reddish yellow or orange tint.

With this pure substance, the following determinations were made (all weighings were made with a microbalance sensitive to 0.000001 Gm.):

(1) The substance, 0.0009625 Gm. was mixed with approximately 20 cc. of ether, 3 cc. of saturated ethereal solution of paradimethylaminobenzaldehyde was added, then 10 drops of concentrated hydrochloric acid. This was shaken two minutes. A little water was added, shaken briefly, then 4 cc. of saturated aqueous solution of sodium acetate was added, and the substance again shaken. The colored aqueous solution was drawn off. Shake-outs were repeated in the same way, from 5 to 8 drops of hydrochloric acid and 3 cc. of sodium acetate solution being used until no more color could be extracted. The final volume was 102 cc. This was compared in the colorimeter (Klett) with the standard phenolphthalein solution previously described. Standard 20, R = 8, 8.5, 7.9, 8.2, average, 8.15. Since 0.943 mg. was present in 100 cc. $\left(\frac{100}{102} \times 0.962\right)$, $\frac{8.15}{20} \times 0.943 = 0.384 =$ mg. per hundred cubic centimeters equivalent to the standard phenolphthalein solution.

On three more occasions, shortly after this, with the same procedure and varying amounts of mesobilirubinogen, the following figures were obtained:

0.0006497 Gm. to 100 cc. S20 R 11.5, 10.3, 12.4, 11.5 av. 11.4, 0.370 mg. per 100 cc.
0.001980 Gm. to 250 cc. S20 R 9.5, 8.9, 10.0, 9.4 av. 9.4. 0.371 mg. per 100 cc.
0.001935 Gm. to 250 cc. S20 R 9.6, 10.2, 10.4, 10.5 av. 10.2. 0.394 mg. per 100 cc.

The average of these four determinations was: 0.379 mg. per hundred cubic centimeters = to the phenolphthalein standard. (S indicates standard; R, urobilinogen solution.)

(2) Three more determinations were obtained in the same way, except that the crystalline substance was dissolved in 20 cc. of 10 per cent sodium hydroxide, which, with 20 cc. of water was added, with shaking, to 20 cc. of 20 per cent ferrous sulphate in a small Erlenmeyer flask. This was evacuated and left in the dark for one hour. At the end of this period, 5 or 6 cc. of the filtrate, varying in different instances, was acidified with 20 per cent acetic acid and shaken out with a large volume of ether (from 20 to 30 cc.). The procedure, thenceforth, was the same as that already described. The values obtained were: 0.429, 0.430, 0.429 mg. per hundred cubic centimeters = to phenolphthalein standard. It seemed evident that a moderate, though constant, loss occurred in these instances. Deterioration of the substance was not believed to be responsible since the first determination was carried out within an hour of the last of those already mentioned. The primary extraction with ether was complete, and all of the color was extracted from the ether so that only the ferrous hydroxide precipitate was left in question. According to Terwen, the ferrous hydroxide does not adsorb any urobilinogen and it is true that extraction of alcohol of this precipitate has failed to show color with Ehrlich's reagent. Adler stated that the intensity of red in alcoholic solution increases to a maximum only after from twenty to twenty-five minutes, and that in alcoholic solution certain proportions of alcohol and water are optimal. Since the color is entirely removed in the present method by repeated condensations into a final aqueous solution, these conditions are not parallel, so that no interference is believed to have arisen in this way. A fourth determination was made in which 20 cc. of urobilin-free urine was substituted for the water as in the foregoing instance. Here 0.004264 Gm. of mesobilirubinogen were dissolved in 60 cc., reduced one hour, then 5 cc. of filtrate acidified, extracted and

finally diluted to 250 cc. S = 10, R = 28.7, 28.4, 28.6, 28.5, average 28.5. Five cubic centimeters of filtrate contained 0.3553 mg. diluted to 250 cc.

$\simeq$ 0.142 mg. in 100 cc. $\times \frac{28.5}{10.0}$ = .404 mg. /100 cc. $\simeq$ phenolphthalein standard.

(*b*) Since Fischer considered the molecular weights of bilirubin and hemibilirubin to be relatively the same, it was believed that a constant equivalent color value from varying amounts of pure bilirubin reduced in different experiments, would be of considerable assistance in standardizing the phenolphthalein solution. With this in mind, the following determinations were carried out (this investigation was made prior to that previously described): 0.0598 Gm. of pure bilirubin (Eastman) dissolved in 50 cc. of tenth-normal sodium hydroxide and 10 Gm. of 5 per cent sodium amalgam were added. (The balance used for this weighing was sensitive only to 0.1 mg.) One hour later, 10 Gm. more of sodium amalgam was added. Then at the intervals subsequently given small measured portions (from 0.2 to 0.5 cc.) of the filtrate were removed, acidified with 20 per cent acetic and all of the aldehyde reacting substance shaken out as in the routine procedure and compared with the phenolphthalein standard. The equivalent values in milligrams per hundred cubic centimeters at the different periods are given under (*a*). Under (*b*) and (*c*) are given the results of two similar sets of determinations, with the primary amount of bilirubin used in each instance.

(*a*)		(*b*)		(*c*)	
0.0598 Gm. bilirubin reduced.		0.0302 Gm.		0.04265 Gm.	
2 hrs.	0.797	1 hr.	1.2	1 hr.	0.742
3 hrs.	0.542	2 hrs.	0.906	2¼ hrs.	0.75
4 hrs.	0.422	3 hrs.	0.906	3½ hrs.	0.68
6½ hrs.	0.478	4 hrs.	0.98	4½ hrs.	0.88
8 hrs.	0.458	6½ hrs.	1.2		
21 hrs.	0.717				
24 hrs.	0.917				
72 hrs.	1.315				

From this it was evident that no constant value might be obtained, although it was considered significant that the lowest value obtained, 0.422, was obtained with the largest sample of bilirubin, and hence was liable to the smallest error, particularly as regards the influence of oxidation; this value was of the same magnitude as those obtained in the determinations with mesobilirubinogen.

(*c*) "Urobilin" was isolated from feces according to the procedure described by Terwen. This was reduced in varying small amounts on three occasions with ferrous hydroxide. The values in milligrams per hundred cubic centimeters $\simeq$ to the standard were 0.44, 0.40 and 0.39. In these determinations the filtrate was analyzed at one-half hour intervals for several hours and the maximum amount of color found used in calculation. The optimum period varied from forty-five to ninety minutes.

After consideration of all of the foregoing observations it is believed that the value 0.4 first given by Terwen, is satisfactory for clinical usage. On the basis of theory, it was first believed that 0.3 should be the correct figure, since the ratio of the molecular weights of hemibilirubin and of Terwen's urobilin are 3 : 4. That the values are, however, practically the same may be explained either on the basis

of a dipyrrol impurity in Terwen's material or an error in the molecular weight determination of 758 (micromethod, boiling point of camphor).

2. Determinations with the clinical quantitative method previously described under varying conditions.

(*a*) Urine.

Primary dilution 1.5 second dilution 5, S = 10, R = 10

$$1.5 \times 5 \times \frac{10}{10} \times 0.4 = 3 \text{ mg. per 100 cc.}$$

Same, except with primary dilution with calcium hydroxide solution, as for precipitation of bilirubin.

$$1.5 \times 1.5 \times 4 \times \frac{10}{12} \times 0.4 = 3 \text{ mg. per 100 cc.}$$

(*b*) With different amounts of filtrate

5 cc.

$$1.5 \times 3 \times \frac{10}{10} \times 0.4 = 1.8 \text{ mg. per 100 cc.}$$

50 cc.

$$1.5 \times 1 \times \frac{20}{6.7} \times 0.3 = 1.76 \text{ mg. per 100 cc.}$$

(*c*) After standing with salicylic acid preservative. (Terwen was able to show that salicylic acid alone did not have any influence on the values obtained.)

The urine contained 1.76 mg. in 100 cc.

Five days later, it contained 1.45 mg. in 100 cc.

(*d*) Duplicate determinations on the same stool specimens with different weighings and extractions.

(1) 53.3 mg. per 100 Gm.
60 mg. per 100 Gm.

(2) 195.5 mg. per 100 Gm.
209 mg. per 100 Gm.

(3) 269.5 mg. per 100 Gm. No urobilin band in filtrate.
221.5 mg. per 100 Gm. Definite medium faint alkaline urobilin band in filtrate (500-510).

(*e*) Supplementary reduction with sodium amalgam.

Sample of feces. Primary dilution 60, final dilution 16, S = 10, R = 18.

$$60 \times 16 \times \frac{10}{18} \times 0.4 = 213.2 \text{ mg. per 100 Gm.}$$

Same filtrate allowed to stand in sunlight until a definite urobilin band appeared, then 10 cc. reduced with 1 Gm. of 5 per cent sodium amalgam, five minutes (at the end of this period, colorless and without urobilin band).

$$60 \times 13 \times \frac{10}{15} \times 0.4 = 208 \text{ mg. per 100 Gm.}$$

A second stool filtrate with a medium heavy urobilin band:

$$40 \times 13 \times \frac{10}{12} \times 0.4 = 173.3 \text{ mg. per 100 Gm.}$$

One gram of 5 per cent sodium amalgam added to about 10 cc. of the same filtrate. After twenty minutes, urobilin band is hardly discernible.

$$40 \times 14 \times \frac{10}{11} \times 0.4 = 201.8 \text{ mg. per 100 Gm.}$$

3. Efficiency of ether extraction for large amounts of filtrate. (Terwen was able to show that with small amounts of filtrate one ether extraction sufficed to remove 96 per cent of the urobilinogen.)

On two occasions, 50 cc. of filtrate from urines rich in urobilin were acidified and extracted, once with ether in the ordinary way. The aqueous fractions were then acidified with sulphuric acid and saturated with solid ammonium sulphate. They were then extracted with from 10 to 15 cc. of amyl alcohol. Only a very faint urobilin band was demonstrable in either of these extracts, which, considering their concentration, indicates satisfactory extraction with one shake-out.

4. Quantitative range of method. By concentration of large amounts of filtrate, the method becomes very sensitive. Thus, 1,970 cc. of urine was found to contain 1.044 mg., when 50 cc. of filtrate was concentrated to 6 cc., or 0.053 mg. per hundred cubic centimeters. On another occasion, 1,760 cc. of urine contained 1.026 mg. or 0.05 mg. per hundred cubic centimeters, after 50 cc. of filtrate was diluted to 10. The color in this instance was slightly too yellowish for accurate comparison. In general, the method is believed to be sensitive to between 0.05 and 0.1 mg. per hundred cubic centimeters, the variation depending on the concentration employed.

CLINICAL OBSERVATIONS

In the following pages are summarized the observations in a series of normal and abnormal persons on whom the foregoing method was employed. Stools were collected as a routine measure for four days. Single investigations of urine were usually made for the same period; if consecutive, forty-eight hour specimens were utilized. In any case, the reported value is an average twenty-four hour amount. Hemoglobin estimations were made with a Klett colorimeter and Newcomer disk which was checked gasometrically. Reticulocyte counts were done by the smear method. Van den Bergh's original qualitative technic was used. The quantitative procedure was not employed. Bernheim's icterus index method was used with a standard disk for a Klett colorimeter (supplied by Klett and Company). The range of normal with this apparatus was from 5 to 8. Even when serum is obtained with the greatest care, small amounts of hemoglobin are usually discernible with the spectroscope, and this is undoubtedly responsible for a small undetermined error. Bilirubin in urine was recognized by the Gmelin reaction carried out on filter paper.

In employing the foregoing values, 175 mg. per day for feces was considered the upper limit of normal for females and 250 mg. per day for males. It is probable that greater uniformity would be attained with a larger and more representative normal series. The females were nurses on hospital duty, several of whom had slightly subnormal hemoglobin percentages and erythrocyte counts. The males were ambulatory patients in the hospital for relatively minor conditions, believed irrelevant, although it is not impossible that previous tonsillectomy in one instance may have increased the value. No definite relationship was noted between body weight and elimination of urobilinogen.

The results in the cases of pernicious anemia will be discussed collectively later. In the following paragraphs clinical results are corre-

Urobilinogen Elimination and Other Laboratory Observations

Diagnosis	Sex	Age	Weight	Date	Hemoglobin	Red Blood Cells	Reticulocytes, per Cent	Van den Bergh Icterus Index	Urine, Bilirubin	Urine, Urobilinogen	Stool, Urobilinogen
Normal (1)	M	25	165	5/ 4	14.2	4.44	...	.. ...	0	0.7	192.3
Normal (2)	M	23	163	2/ 4	15.8	4.78	(1 week posttonsillectomy)		0	0.9	245.7
Normal (3)	M	61	150	2/25	13.5	4.22	...	.. ...	0	Trace	217.4
Normal (4)	M	27	192	1/ 6	16.8	4.77	...	.. ...	..	...	.....
				2/ 4	(10 days posttonsillectomy)				0	Trace	174.9
Normal (5)	M	28	150	5/14	....	....	...	.. ...	0	0.5	117.4
Average daily elimination for males											189.5
Normal (6)	F	20	113	5/ 4	13.9	4.9	...	.. ...	0	Trace	54.4
Normal (7)	F	20	155	4/28	12.9	4.14	...	.. ...	0	Trace	162.4
Normal (8)	F	20	107	3/30	14.6	4.38	...	.. ...	0	0.25	134.0
Normal (9)	F	19	174	4/ 1	14.8	4.40	...	.. ...	0	Trace	149.6
Normal (10)	F	22	134	4/ 7	15.0	4.61	...	.. ...	0	Trace	107.7
Normal (11)	F	20	123	4/15	13.1	3.96	...	.. ...	0	0.4	89.6
Normal (12)	F	21	164	4/19	13.9	4.10	...	.. ...	0	Trace	122.3
Normal (13)	F	20	127	4/24	13.5	4.09	...	.. ...	0	Trace	83.4
Average daily elimination for females											112.9
Average daily elimination for both sexes											151.2
Secondary anemia (1)	F	17	102	12/13	11.8	3.58					
				12/29	....	....	...	.. 7.5	0	Trace	66.2
Secondary anemia (2)	F	33	117	12/ 3	7.0	2.9	0.4	.. 5.0	0	0.9	18.3
Secondary anemia (3)	F	29	112	12/30	9.5	2.73	0.2	.. 8.0	0	0.8	35.5
Secondary anemia (4)	F	19	106	5/ 8	12.3	3.72	...	.. ...	..	0.0	51.7
				1929							
Pernicious anemia (1)	M	63	144	4/30	12.2	3.71					
				11/27	11.8	2.49	0.4				
				11/30	....	....	0.4				
				12/ 2	....	....	...	.. ...	0	6.87	127.0
				12/ 4	....	....	3.2			(Six day collection)	
				12/ 7	....	....	... Delayed	9.5			
Pernicious anemia (2)	P	59	150	3/ 3	4.4	0.87	0.8	.. 27.0	0	3.4 (48 hour collection)	1179.5
Pernicious anemia (3)	M	54	150	1/22	5.8	1.12	0.2				
				1/24	....	....	0.8	.. 10.7			
				1/27	....	....	1.6	.. ...	0		
				1/29	6.0	1.33	1.6	.. ...	..	1.2	902.8
				2/ 1	6.0	1.78	18.6				
				2/ 4	7.9	....	9.0				
				2/ 7	8.5	2.56	5.0				
				2/13	11.6						
				2/14	12.5	3.81	0.1	.. ...	..	Trace	290.0
				3/10	16.1	4.84	0.0				
				3/12	....	....	...	.. ...	..	Trace	172.9
Pernicious anemia (4)	F	68	141	3/11	10.9	1.92	0.36				
				3/15	10.4	1.93	...	.. 5.4	0	2.2	260.9
				3/17	....	....	5.2	.. ...	..	1.5	
				3/21	11.2	2.4	4.1				
				3/27	11.2	2.66	3.4	.. ...	..	Trace	
				4/ 3	12.3	2.88	1.3	.. ...	..	...	70.4
				4/ 9	12.2	3.07					
Pernicious anemia (5)	F	56	98	3/ 6	3.9	1.03	2.6	.. 15.0			
				3/11	....	....	4.4	.. ...	0	1.8	279.0
				3/13	4.1	1.49					
				3/15	....	....	19.0				
				3/20	....	....	...	.. ...	..	27.2	
				3/22	8.0	2.4	6.3	.. ...	..	8.1	357.7
				3/26	....	....	...	.. ...	..	1.5	
				4/ 2	....	....	...	.. ...	..	Trace	
				4/ 4	8.5	3.16	1.9	.. ...	..	0.0	
				4/ 8	....	....	0.95	.. ...	..	0.0	
				4/10	9.0	3.65	1.0	.. ...	..	0.85	177.4

Urobilinogen Elimination and Other Laboratory Observations—Continued

Diagnosis	Sex	Age	Weight	Date	Hemoglobin	Red Blood Cells	Reticulocytes, Per Cent	Van den Bergh Index		Urine, Bilirubin	Urine, Urobilin	Stool, Urobilin
Pernicious anemia (6)	M	74	170	1/11	6.2	1.32						
				1/13	....	....	0.4	Delayed	12.5			
				1/14	....	....	0.6	..	...	0	18.5	
				1/16	....	....	0.3	..	...	..	...	249.1
				1/17	....	....	0.2					
				1/18	7.0	1.41						
				1/21	7.2	1.66	10.6	..	...	..	2.7	
				1/23	....	....	...	..	...	..	0.6	484.7
				1/24	7.7	1.89	9.8					
				1/29	8.0	2.14	9.6					
				1/31	8.0	2.57						
				2/ 4	....	....	1.0					
				2/ 6	8.3	2.29						
				2/14	11.8	2.9	0.5					
				2/20	12.7	3.07						
				2/27	13.3	3.15						
				3/ 6	14.0	3.53						
				3/13	14.4	4.07						
				5/13	....	....	...	..	...	..	0.68	216.5
Pernicious anemia (7)	F	62	138	1/ 6	4.0	0.83	1.0	Delayed	15.0			
				1/ 8	....	....	1.2	..	...	0	81.5	..
				1/ 9	....	....	0.7					
				1/10	4.2	0.96	1.8	..	...	..	27.9	185.2*
				1/13	4.2	0.89	8.1					
				1/16	....	....	8.0					
				1/21	6.7	1.52	7.4					
				1/24	7.6	2.0	3.4					
				1/28	7.7	1.92	1.8	..	...	..	4.9	
				1/31	7.7	2.06	...	..	3.0	..	4.5	1143.6
				2/ 4	8.0	2.12						
				2/ 8	....	....	0.65					
				2/11	....	....	...	..	...	..	0.4	
				2/12	9.4	3.01	0.5	..	...	..	...	92.7
				2/19	8.9	2.93	...	..	...	..	Trace	
				2/26	9.7	3.28						
				4/ 5	12.1	3.64	...	..	...	..	Trace	(Single specimen only)
Pernicious anemia (8)	M	75	130	5/ 1	4.4	0.98	0.27					
				5/ 3	....	....	...	..	...	..	10.9	
				5/ 4	3.8	0.89	0.85	..	11.7	0	11.7	
				5/ 6	....	....	...	..	...	..	...	535.2
				5/ 9	3.9	0.94	2.6	..	...	..	4.25	
				5/10	....	....	...	..	...	..	6.9	
				5/12	....	....	10.1	..	...	..	18.2	
				5/15	4.9	1.37	13.8	..	...	..	7.45	325.6
				5/16	....	....	...	..	...	..	13.2	
				5/18	....	....	...	..	...	..	28.1	
				5/19	5.4	1.5	9.8	..	...	..	32.4	
				5/20	6.0	1.9	9.4					
				5/24	....	....	...	..	...	..	21.0	
				5/26	6.6	2.15	1.7	..	...	..	5.6	
				5/28	....	....	...	..	...	..	1.5	
				5/29	7.7	2.35	0.9	..	...	..	0.4	
				5/30	....	....	...	..	...	..	0.9	
				6/ 3	10.7	3.2	1.1	..	...	..	Trace	
				6/ 5	....	....	...	..	...	..	Trace	
				6/ 9	10.9	3.39	0.5					
Probable mild congenital hemolytic jaundice	F	36	120	12/ 5	14.6	4.68	...	Faint	8.3	0	0.9	
				12/ 8	....	....	...	Delayed	...	..	2.7	234.1
Mild encephalitis lethargica	F	21	157	12/22	14.5	4.38	...	..	...	0	2.05	142.4
				1928								
Hypertension and polycythemia (Gaisbock ?) after treatment with phenylhydrazine	F	53	120	10/15	16.2	5.40						
				1929								
				8/14	18.5	6.85						
				8/23	20.3	6.48	0.6					
				8/26	18.5	6.26						
				8/31	16.1	5.18						
				12/10	17.2	5.28	Phenylhydrazine intermittently					
				12/19	19.0	5.34						
				12/27	16.0	5.48						
				1930								
				1/20	15.0	3.71						
				3/ 7	18.4	6.06						
				4/18	15.5	4.85						
				4/24	....	....	...	Weak and indirect	9.9	0	0.95	243.8
				4/28	15.8	4.92						

* Relatively very small amount of stool in four day collection.

Urobilinogen Elimination and Other Laboratory Observations—Continued

Diagnosis	Sex	Age	Weight	Date	Hemoglobin	Red Blood Cells	Reticulocytes, per Cent	Van den Bergh Index	Icterus	Urine, Bilirubin	Urine, Urobilin	Stool, Urobilin
Chronic cholecystitis (1)	M	27	160	2/ 6	16.8	5.02	0.25	..	9.3			
				2/17	....	....	...	..	...	0	0.9	301.5
Chronic cholecystitis (2)	M	47	155	3/ 6	14.2	4.07						
				3/ 9	....	....	...	..	...	0	1.0	190.2
Chronic cholecystitis (3)	F	36	140	3/15	....	....	...	Delayed	33.0			
				3/18	13.9	3.99	...	..	...	+	0.65 (48 hour collection only)	633.6
Chronic cholecystitis (4)	F	45	150	3/ 4	13.6	3.60	...	..	8.0	0	7.25 (48 hour collection only)	50.6
Chronic cholecystitis (5)	F	56	210	3/19	16.0	4.89	0.5	..	...	0	1.07	226.2
Chronic cholecystitis (6)	F	58	150	1/17	Acute exacerbation with fever					0	23.6	194.3
				1/24	14.1	3.74	0.8	Afebrile	7.5	..	2.8	82.2
Chronic cholecystitis (7)	M	50	165	2/ 3	16.6	4.70						
				3/ 3	....	....	...	..	...	0	Trace	208.1
Catarrhal jaundice (1)	F	16	140	4/ 3	14.1	4.29	0.86	Biphasic delayed	52.0			
				4/ 5	....	....	...	..	...	Trace	69.0	
				4/ 7	Symptoms and jaundice subsiding					0	16.8	221.3
				4/12	Feels well; no jaundice				...	0	2.65 (48 hour collection only)	
				5/28	Recurrent deep jaundice				...	..	4.3 (48 hour collection only)	4.6
				5/30	....	....	...	..	...	..	7.0	
Catarrhal jaundice (2)	F	12	70	3/ 5	15.8	4.99	2.1	..	150			
				3/19	Symptoms and jaundice subsiding					+	26.5	
				3/21	....	....	...	..	...	+	16.7	255.5
				3/26	....	....	...	Delayed	29			
				3/30	Jaundice has disappeared				...	0	1.2	
				7/ 1	Feels well; no jaundice				...	0	0.6	
Catarrhal jaundice (3)	M	47	150	11/ 1	16.1	4.3	...	Biphasic prompt				
				11/ 8	....	....	...	..	...	+++	4.3*	
				11/ 9	....	....	...	..	...	+++	2.0	6.9*
				11/10	....	....	...	..	...	+++	21.4	12.7
				11/11	....	....	...	..	...	+++	1.9	10.4
				11/12	....	....	...	..	...	+++	2.9	7.2
				11/13	....	....	...	..	...	+++	4.0	9.0
				11/15	Cholecystotomy							
										Average	8.46	9.24
				12/ 1	....	....	...	..	...	+	61.2*	
				12/ 2	....	....	...	..	...	+	46.0	
				12/ 3	....	....	...	..	...	+	39.0	
				12/ 4	....	....	...	..	...	+	28.4	
				12/ 7	....	....	...	..	53			
										Average	43.6	38.5
				1/ 4	....	....	...	..	25	0	2.09	174.5
				7/15	Condition good							
Pregnancy (1)	F	34	130	2/18	10.9	3.16	2.8					
				2/24	Mild vomiting of pregnancy; symptoms have subsided after 2 weeks in hospital					0	1.2	152.0
Pregnancy (2)	F	36	220	1/ 9	11.8	3.46	...	Biphasic	90.0			
				1/12	....	....	2.9					
				1/15	....	....	2.2	..	...	..	109.8	555.1
				1/20	11.9	3.89						
				1/23	One week after delivery				15.0	..	6.9	286.2
				4/14	12.7	3.96	0.67	..	6.9			
				4/18	....	....	...	..	...	..	1.4	150.5
Probable cirrhosis of the liver	M	57	188	5/19	10.1	2.86	...	Indirect weakly positive	12.2			
				5/23	....	....	...		...	..	10.1*	
				5/25	....	....	...	..	...	0	1.87	633.7
				5/29	....	....	...	..	...	..	2.7*	
				5/31	....	....	...	..	...	..	4.32	170.7

* Forty-eight hour collection.

lated to some extent with the figures for the cases represented in the table.

Probable Mild Congenital Hemolytic Icterus.—The patient had always had a dark, sallow skin. Anemia was noted by a physician fifteen years before. None of the patient's relatives had ever had jaundice or a large spleen, so far as was known. There was some dull aching pain in the left upper part of the abdomen. On inspiration, the spleen was felt 1.5 cm. below the margin of the rib in the left midclavicular line. There were 10,000 leukocytes, 62 per cent neutrophils and 3.5 per cent eosinophils. Moderate anisocytosis with definite predominance of smaller hyperchromatic erythrocytes was noted. In the fragility tests, hemolysis began at 0.46 per cent and was complete at 0.34 per cent; in a control experiment it began at 0.44 per cent and was complete at 0.34 per cent. (Hemolysis of the patient's cells was much more complete between 0.44 per cent and 0.38 per cent than in control.) The Wassermann reaction was negative.

Chronic Cholecystitis.—Case 1.—The patient suffered from a distress suggestive of a chronic disease of the gallbladder. He had had typhoid fever fifteen years before. The present symptoms dated to vaccination for typhoid three years before, following which the patient was quite ill and lost considerable weight. Brown pigmentation of the skin, more marked on the unexposed surfaces, appeared at intervals, but it never disappeared entirely. The Graham-Cole test was negative.

Possibly the increased urobilinogen in the stool in this instance is to be explained by a persistent typhoid infection; unfortunately, stools and urine were not examined for typhoid bacilli.

Case 2.—Cholecystectomy was performed. The gallbladder exhibited a mild chronic cholecystitis. Postoperative pneumonia developed, and the patient died. The liver exhibited no evidence of disease at necropsy other than mild cloudy swelling.

Case 3.—The patient suffered from a colicky pain in the right upper quadrant of the abdomen two years before, with jaundice. Severe colic of several days' duration with jaundice occurred in the present attack. The pain had disappeared, and jaundice was definitely lighter at the time of the urobilin estimations. The Graham-Cole test showed a pathologic gallbladder.

Mueller first observed the definite increase of urobilinogen in the stools after release of an obstructive jaundice, whether catarrhal or otherwise. This was quite definite in this instance and was also observed in the cases of catarrhal jaundice. The urobilinogen in the urine was not increased; this coincides well with the view of Wallace and Diamond, who believed that urobilinuria occurred with jaundice due to disease of the liver, not with that due to simple extrahepatic obstruction. The foregoing case is the only instance in the present series which bears on this point. Experimentally, Elman and McMaster found urobilinuria promptly after obstruction of the common duct. More clinical study is necessary to determine the value of urobilinuria in the differentiation of these two divisions of jaundice, i.e., extrahepatic and hepatic obstructive jaundice. Compared with catarrhal jaundice, believed to be of the latter type, the foregoing case points to the value

of urobilinuria in differentiation, since cases of catarrhal jaundice, when clearing up, present marked urobilinuria.

CASE 4.—The patient had had repeated gallbladder colics in the past twenty-five years. The present attack was much more severe. At first there were 39,000 leukocytes. The abdomen was distended, very tender, with some rigidity (lower part of the abdomen as well as above). The temperature varied from 102 to 103 F. There was improvement after several days of supportive therapy. The temperature was normal. The amount of urobilin was estimated at this time. A very small amount of stool was obtained. Extensive fat necrosis was found at laparotomy; a markedly diseased gallbladder that contained stones was removed. The convalescence was very difficult and prolonged.

The urobilinuria in this instance was believed to be due to toxic injury to the liver.

CASE 5.—Cholelithiasis and pathologic gallbladder were diagnosed by the Graham-Cole method. Repeated colics, occasionally with jaundice, had occurred in the past twenty years. Cholecystectomy was performed, and the liver was found to be apparently normal.

In this case, the moderately increased urobilin in the stool is unexplained; either the size of the patient or possibly the mild increased destruction of the blood secondary to infection is to be considered.

CASE 6.—The patient had had recurrent gallstone colic, and acute exacerbation with severe pain and rigidity in the right upper quadrant; the temperature was 103. There were 20,800 leukocytes. A Graham-Cole roentgenogram made previously suggested pathologic gallbladder. Estimations of the urobilinogen were made at this time and again after improvement following rest in bed and supportive measures. The temperature was normal; the pain ceased.

This illustrates the effect of acute infection on the liver. The relatively small amount of urobilinuria persisting after the temperature became normal probably indicates mild residual injury to the liver. At laparotomy at this time the gallbladder still contained considerable purulent exudate and was only drained. The liver showed no evidence of disease.

CASE 7.—Cholecystectomy was performed, and a moderately diseased gallbladder found. The liver was normal in appearance. Convalescence was rapid.

Catarrhal Jaundice.—CASE 1.—The patient had had mild jaundice of five days' duration, which was subsiding when seen at the time of the first examination; the symptoms were also disappearing (nausea and vomiting, anorexia and constipation). The stools had been light colored at the onset of the jaundice. At the time the patient was seen the increased urobilin in the stool and marked urobilinuria with the stool-urine ratio of 5:1, permitted a diagnosis of injury to the liver in the stage of recovery. The patient went home apparently quite recovered. It is important to note that the urobilin in the urine was still abnormally elevated, in spite of the apparent complete recovery. The patient returned in six weeks with deep jaundice; at this time the amount of urobilin in the stool and urine were

both low, but the ratio was about 1 : 1, indicating severe damage to the liver. The stools were clay-colored. The patient was much more ill than previously. The temperature rose daily to 101 and 102 F. There was no pain, but terminal vomiting and a hemorrhagic tendency were present. The patient was toxic and irrational. She died in coma. Permission for necropsy was refused. The clinical diagnosis was subacute yellow atrophy.

CASE 2.—The first estimations of the urobilin were made when the symptoms and jaundice were subsiding. Again the urobilinogen in the stool was increased, and the stool-urine ratio was low, about 11 : 1, indicating injury to the liver. With complete subjective recovery and disappearance of jaundice, the urobilinogen in the urine was normal. This patient was entirely healthy four months later.

CASE 3.—The patient was admitted to the hospital on Nov. 1, 1929. Painless jaundice had been present for three weeks. There were anorexia and mild constipation. Fifteen years before the patient had had epigastric distress of two weeks' duration without jaundice. When admitted he had deep jaundice. The edge of the liver was 5 cm. lower than normal, smooth and firm. The stools were clay-colored. The contents of the stomach showed free hydrochloric acid 54, and occult blood was present. Occult blood was found in several stools. A roentgenogram of the gastro-intestinal tract showed a defect typical of a small duodenal ulcer. Leucine and tyrosine were absent in two urinalyses, but were present on the third examination with correct solubility tests. Bromsulphalein retention was 45 per cent in thirty minutes; iso-iodeikon showed 40 per cent retention; the gallbladder was poorly visualized. Operation was preceded by daily administration intravenously of dextrose and calcium chloride. At laparotomy, the liver was found enlarged, swollen, and reddish; there were few adhesions around the gallbladder and a definite small duodenal ulcer. No obstruction to the common duct was found. The gallbladder was drained. There was considerable drainage of dark bile subsequently, followed by definite improvement. Modified Sippy ulcer management was begun. On Jan. 3, 1930, the patient was up and about and felt very well. The liver was not palpable, and there was only very slight skin jaundice. The total duration of the jaundice was about three months. On July 15, the patient's condition was good, and there had been no recurrence of jaundice.

The very low stool-urine urobilinogen ratio (about 1 : 1), persisting for some time even after partial resumption of the flow of bile, indicated severe injury to the liver. This, with the long duration of the jaundice and the occurrence of leucine and tyrosine in the urine, necessitated a poor prognosis. Recovery was believed to be aided by the intravenous administration of dextrose and drainage of the gallbladder; whether the drainage of bile was due to coincidental beginning recovery or to a suction action on the liver, remains a mystery. Following the disappearance of jaundice, a practically normal stool-urine ratio is noted, with urine urobilinogen still slightly increased.

Pregnancy.—CASE 1.—The patient, pregnant about four months, had mild toxic vomiting with secondary anemia. Estimations of the urobilinogen were made after ten days of hospitalization, with considerable improvement.

CASE 2.—The patient was seven and one-half months pregnant. She suffered from moderate jaundice, daily colicky pain in the right upper quadrant and vomiting. There was no fever. She had had similar attacks previously. The gall-

bladder was drained two years before while she was seven months pregnant; she did not think that stones were found. Moderate albuminuria was present. There were 5,850 leukocytes, 71 per cent neutrophils, and moderate anisocytosis. Immediate marked improvement followed spontaneous labor.

In spite of the probable existence of disease of the gallbladder in this instance and the possibility of a stone in the common duct, the estimations of urobilinogen pointed to increased destruction of the blood, borne out by the regenerative anemia and to considerable injury of the liver because of the low stool-urine ratio. This approached normal soon after delivery. It was believed that the observations could be explained on the basis of a toxemia of pregnancy.

Pernicious Anemia.—Case 1.—The disease was recognized one year prior to the patient's admission to the hospital. Liver extract in relatively small doses was given during the last eight months. There were definite numbness and tingling of the extremities. The patient did not have "sore tongue." No free hydrochloric acid was found in the contents of the stomach. Erythrocytes showed marked macro-anisocytosis and hyperchromasia. There were 4,200 leukocytes and 44 per cent lymphocytes. The neutrophils exhibited a moderate shift to the right. The color index was 1.5. Intensive liver therapy was begun on Nov. 27, 1929, with only moderate response. The patient left the hospital against advice on December 12. The condition was said to be unimproved four months later; blood smears showed definite macro-anisocytosis.

Case 2.—Weakness, yellow skin, sore tongue, numbness and tingling had been noted in the past year. The tongue was smooth. There was a loud blowing systolic murmur at the apex of the heart. The erythrocytes showed marked hyperchromasa and macro-anisocytosis. There were frequent "pernicious anemia" neutrophils. Occasional normoblasts were seen at times with multiple nuclear buds; there were occasional myelocytes, 6,250 leukocytes and 67 per cent neutrophils. The patient was extremely weak, and suffered from fever and vomiting. Liver extract equivalent to about 800 Gm. of liver was given by rectum. The patient died three hours after a transfusion of 500 cc. of citrated blood. Necropsy showed marked arteriosclerosis with extensive coronary thickening and some fibrosis cordis. Deeply pigmented bile was seen in the gallbladder. The liver showed no gross disease. The spleen weighed 300 Gm., and was firm and dark red. The bone-marrow shaft of the femur was definitely hyperplastic (red). Microscopic examination showed an occasional hypertrophic Kupffer cell, with infrequent erythrophagocytosis, very little hemosiderin, markedly hyperplastic bone-marrow, approximately equally myeloblastic and erythro-megaloblastic, diffuse pulp congestion in the spleen and slight hemosiderosis.

Case 3.—The patient had had epigastric distress suggestive of peptic ulcer for the past several months, weakness, some numbness and tingling in the extremities for two months, a smooth tongue, pale yellowish skin and impaired sense of vibration. Examination of the blood showed marked macro-anisocytosis; dispersion of the Arneth count to the right and left, with occasional typical neutrophils, 2,500 leukocytes with 43.5 per cent lymphocytes and 5 per cent eosinophils. There was no free hydrochloric acid. Marked improvement followed intensive liver therapy (500 Gm. of cooked liver daily).

CASE 4.—The patient had had weakness, sore tongue and substernal pain for two years. Definite macro-anisocytosis, poikilocytosis, slight polychromasia and occasional normoblasts were noted. There was no free hydrochloric acid. Improvement of blood was shown after daily administration of liver extract equivalent to 500 Gm. of liver. There was considerable subjective improvement.

CASE 5.—The patient had had pale yellow skin varying in degree for the past two years. A sore tongue and mouth, weakness and dyspnea had been present for the past year. Numbness and tingling were felt in the extremities for the past few weeks. Erythrocytes showed hyperchomasia, macro-anisocytosis and marked poikilocytosis. There were occasional normoblasts, myelocytes and promyelocytes; with 2,600 leukocytes and 41.5 per cent lymphocytes, and later 5,600 leukocytes and 37 per cent lymphocytes. Definite "pernicious anemia" neutrophils were present. Liver or liver extract equivalent, 500 Gm., daily was given (beginning March 6, 1930). On June 21, the patient felt quite well, and had a good appetite.

CASE 6.—The patient complained of dyspnea, weakness and sore tongue. There were 3,650 leukocytes and 46.5 per cent lymphocytes; the neutrophils showed a marked shift to the right. Marked macro-anisocytosis and hyperchromasia and some poikilocytosis were present. The Minot-Murphy diet was begun on Jan. 11, 1930 (500 Gm. of liver daily), and caused marked improvement. On April 4, the patient's condition was good. The liver therapy was continued (from 200 to 300 Gm. daily).

CASE 7.—The patient suffered from progressive weakness and dyspnea for one year. The skin was pale and yellowish. There were 4,350 leukocytes and 49 per cent lymphocytes. The neutrophils showed a shift to the right. Marked hyperchromasia and macro-anisocytosis, and poikilocytosis were present. There were occasional normoblasts, some with multiple nuclear buds. Liver extract, equivalent to from 400 to 500 Gm. of liver, was given daily. Later, this therapy was supplemented by cooked whole liver. On April 5, 1930, the patient felt fairly well but was still somewhat weak. The blood has improved as shown.

CASE 8.—The patient was extremely weak and irrational, with pale yellow skin and a moderately smooth tongue. There were 2,750 leukocytes with 57.5 per cent lymphocytes, 8 per cent eosinophils. The erythrocytes showed marked macro-anisocytosis, poikilocytosis and hyperchromasia. There were frequent normoblasts with multiple nuclear buds, some basophilic stippling and occasional "pernicious anemia" neutrophils. Liver extract equivalent to from 400 to 500 Gm. of liver was given daily, with some difficulty. There was considerable improvement. The patient left the hospital on June 9, 1930.

The repeated estimation of urobilinogen in the foregoing cases of pernicious anemia in which liver therapy was used suggested that they could be divided into two groups in which the absence or persistence of urobilinuria after the reticulocyte crisis was correlated with the rate of increase of erythrocytes and hemoglobin. Patients in whom urobilinuria disappeared at or before the reticulocyte crisis (cases 3, 4 and 6 in table) exhibited an increase of hemoglobin over a considerable period at the average rate of 0.143 Gm. per day and of 0.055 millions of erythrocytes per day, while those in whom urobilinuria persisted for even a short time after the reticulocyte crisis (cases 5, 7 and 8), the

corresponding values were 0.120 and 0.048. Case 1 was not included in the latter group, because the patient had been on liver therapy for a much longer period, and was therefore not comparable. It was significant, however, that while his blood failed to show improvement, urobilinuria was definite, with normal urobilin in the stool.

In these two groups the average elevation of hemoglobin reached in the first (with disappearance of urobilinuria) was 14.2 Gm. and of red blood cells 3.99 millions; this was observed after an average period of forty-seven and seven tenths days. Corresponding values in the second group were 10.7 and 3.56, over an average period of observation of forty-two days. The slight variation in time is not enough to account for the discrepancy, at least as regards the hemoglobin, where correction for the five and seven tenths days brings the value only to eleven and four tenths, while the erythrocyte average corrected is three and eighty-three hundredths. This suggests some interference in the formation of hemoglobin in the second group. It is realized that the number of cases is too small to permit definite conclusions.

The average value for urobilin in the stool in relapse was 557.7 Gm., and in remission induced by liver therapy it was 183.6. This observation, of course, suggests that liver acts by curtailing the increased destruction of the blood. This is the view of Basch, Jungmann, Dyke and Greener, and Schulten. Nothing is known of the factor of urobilin resorption in pernicious anemia, and possibly it is reduced in relation to the fairly constant gastro-intestinal pathologic changes. However, the fact that urobilinuria may often be considerable, as in the present series, is against this conception.

No relation was found to exist between the amounts of urobilinogen in the stool and urine. The urobilinogen in the urine might be increased with a low amount of urobilinogen in the stool as in the first case, or low with a high stool value as in cases 2 and 3. This, obviously, did not support the simple "overflow" theory. Because of the well recognized relation of injury to the liver to urobilinuria and the definite anatomic variations in the liver in relapse and remission, as recently shown by Mettier, together with the present observations, it is suggested that in pernicious anemia urobilinuria is only an evidence of liver derangement.

SUMMARY

Knowledge of the average daily elimination of urobilinogen is often of great aid in the clinical study of jaundice and anemia. This may be obtained by use of the modification of Terwen's method, described herein. The method is not difficult, although any quantitative method applied to feces is necessarily time-consuming. Standardization of the colorimetric procedure is based on the color produced by a chemical individual, mesobilirubinogen, when condensed with paradimethyl-

aminobenzaldehyde by means of hydrochloric acid. This method gives slightly higher values than the original technic of Terwen's. The average urobilinogen in the normal stool was considered by Terwen to be 134, compared with 151.2 in the present series, while the average figures for pernicious anemia are respectively, 455.3 and 554.7 (relapse only). Values for urobilinogen in the stool were found reduced in secondary anemia, unless regenerative with increased destruction of the blood when they were higher. The urobilinogen in the stool was increased for a short time after release of obstructive jaundice, and the stool-urine ratio was reduced with injury to the liver. In pernicious anemia, the rate of increase of hemoglobin and red blood cells in patients treated with liver therapy was somewhat slower if urobilinuria persisted beyond the reticulocyte crisis. Urobilinuria was believed not simply due to overflow with a normal liver, but probably to an actual derangement of the liver, more marked in some instances than others.

CONCLUSIONS

1. A modification of Terwen's method for the estimation of urobilinogen in urine and feces is described, which is believed to be simpler and more efficient than the original procedure.

2. Standardization of the color standard is based on crystalline mesobilirubinogen (Fischer).

3. Results of a series of cases studied with this method are reported and indicate that valuable information may be obtained by its use in the clinical study of jaundice and of the anemias.

4. Persistent urobilinuria after the reticulocyte crisis in cases of pernicious anemia in which liver therapy is used is accompanied by a slower rate of increase of hemoglobin and, to a less marked degree, of erythrocytes.

BIBLIOGRAPHY

Adler, A.: Eine neue Methode der exakt-quantitativen Urobilinogen (mesobilirubinogen) Bestimmung, Deutsches Arch. f. klin. Med. **154**:238, 1927.

Ueber Urobilin: 1. Klinische Methode der (approximativ-) quantitativen urobilin Bestimmung in der Ausscheidungen des Körpers, ibid. **138**:309, 1922.

——and Bressel, M.: Urobilinogen Bestimmung in Stuhl und Harn mittels der neuen Extraktionsmethode, ibid. **155**:326, 1928.

Basch, F.: Ueber den Wirkungsmechanismus der Lebertherapie bei Morbus Biermer, Med. Klin. **24**:1940, 1928.

Bernheim, A. R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia): Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.

Brugsch, T., and Retzlaff, K.: Blutzerfall, Galle und Urobilin. Zur Frage der Gallenfarbstoffbildung aus Blut, Ztschr. f. exper. Path. **11**:508, 1912.

Charnas, D.: Ueber die Darstellung, das Verhalten und die quantitative Bestimmungen des reinen Urobilins und Urobilinogens, Biochem. Ztschr. **20**:401, 1909.

Gegenwärtiger Stand der Urobilin Frage und die Bestimmung des Urobilins, Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **12**:70, 1913.

Ueber kristallisiertes Urobilinogen aus Fäzes, ibid. (supp.) **12**:163, 1913.

Connor, L. A., and Roper, J. C.: The Relations Between Bilirubinemia, Urobilinuria, and Urobilinemia, Arch. Int. Med. **2**:532 (Jan.) 1908.

Dyke, S. G., and Greener, J.: The Reticulocyte Crisis and the Serum Bilirubin in Pernicious Anemia, Lancet **1**:1068, 1928.

Edelmann, M. H.; Halpern, L., and Killian, J. A.: Urobilinuria: Its Prognostic Value in Children with Heart Disease, Am. J. Dis. Child. **39**:711 (April) 1930.

Ehrlich, P.: Ueber die Dimethylamidobenzaldehydereaktion, Deutche med. Wchnschr. 15: cited by Meyer-Betz, 1913.

Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. Quantitative Determination of Urobilin, J. Exper. Med. **41**:503, 1925; IV. Urobilin and the Damaged Liver, ibid. **42**:99, 1925; V. Relations Between Urobilin and Conditions Involving Increased Red Blood Cell Destruction, ibid. **42**:619, 1925.

Eppinger, H.: Die Hepato-Lienalen Erkrankungen, Berlin, Julius Springer, 1920, pp. 76-91.

——and Charnas, D.: Was lehren uns quantitative Urobilin Bestimmung im Stuhl? Ztschr. f. klin. Med. **78**:387, 1913.

Fischer, H.: Zur Kenntnis der Gallenfarbstoffe, Ztschr. f. physiol. Chem. **73**: 204, 1911.

——and Meyer-Betz, F.: Zur Kenntnis der Gallenfarbstoffe: II. Ueber das Urobilinogen des Urins und das Wesen der Ehrlichschen Aldedyreaktion, ibid. **75**:232, 1911.

——and Meyer, P.: Zur Kenntnis der Gallenfarbstoffe: III. Ueber Hemibilirubin und die bei der Oxydation des Hemibilirubins entstehenden Spaltprodukte, ibid. **75**:339, 1911.

——and Röse, H.: Zur Kenntnis der Gallenfarbstoffe, ibid. **82**:391, 1912; Ueber die Konstitution der Bilirubinsäure und des Bilirubins, ibid. **89**:255, 1914; Ueber Mesobilirubin und Mesobilirubinogen, Ztschr. f. Biol. **65**:163, 1914.

Flatow and Brünell: Eine klinische einfache Methode quantitativer Urobilinogen Bestimmung, München. med. Wchnschr., 1913, pp. 234-235.

Fürth, O., and Singer, K.: Ueber die quantitative Bestimmung kleiner Urobilinmengen in den Faeces. Eine Modification der Terwensche Methode, Ztschr. f. d. ges. exper. Med. **6**:152, 1929.

Garrod, A. E., and Hopkins, F. G.: On Urobiiin: I. The Unity of Urobilin, J. Physiol. **20**:112, 1896.

Gerhardt, D.: Ueber Urobilin, Ztschr. f. klin. Med. **32**:303, 1897.

Hijmans van den Bergh, A. A.: Der Gallenfarbstoff im Blute, Leiden, S. C. Van Doesburgh, 1918.

Hoppe-Seyler, G.: Ueber die Auescheidung des Urobilins im Krankheiten, Virchows Arch. f. path. Anat. **124**:30, 1891.

Hueck, W., and Brehme, T.: Experimentelle Untersuchungen zur Urobilinogen Bestimmung nach Eppinger-Charnas, Deutsches Arch. f. klin. Med. **141**:233, 1923.

Jaffe, M.: Beitrag zur Kenntnis der Gallen- und Harn Pigmente, Centralbl. f. d. med. Wissensch., 1868, pp. 241-245.

Ueber die Fluorenscenz des Harnsfarbstoffs, ibid. **7**:177, 1869.

Zur Lehre von der Eigenschaft und den Abstammung der Harnpigmente, Virchows Arch. f. path. Anat. **47**:405, 1869.

Jungmann: Ueber die Wirkungsweise der Leberdiät bei der perniziösen Anämie, Klin. Wchnschr. **7**:441, 1928.

Kammerer, H., and Miller, K.: Zur enterogenen Urobilin Bildung, Deutsches Arch. f. klin. Med. **141**:318, 1923.

Le Nobel, C.: Ueber die Einwirkung von Reduktions mitteln auf Haematin und das Vorkommen der Reduktions Produkte in pathologischen Harne, Arch. f. d. ges. Physiol. **40**:501, 1887.

Lichtenstein, A., and Terwen, A. J.: Ueber die Bereitung und die Eigenschaften von einem möglichst reinem Urobilin Präparat, Deutsches Arch. f. klin. Med. **149**:102, 1925.

Ueber Blutmauserung und Urobilin Ausscheidung, ibid. **149**:113, 1925.

McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: II. Derivation of Urobilin, J. Exper. Med. **41**:513, 1925; III. Absorption of Pigments of Biliary Derivation from the Intestine, ibid. **41**:719, 1925; VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, ibid. **43**:753, 1926.

Physiology and Pathology of Urobilin, Ann. Int. Med. **1**:68, 1927.

Maly: Künstliche Umwandlung von Bilirubin in Harnfarbstoff, Ann. d. Chem. **161**:368, 1871.

Untersuchungen ueber die Gallenfarbstoffe, Dritte Abhandlung, Umwandlung von Bilirubin in Harnfarbstoff, ibid. **163**:77, 1872.

Marcussen, S., and Hansen, S.: On the Determination of Urobilin in the Urine, J. Biol. Chem. **36**:381, 1918.

Mettier, S. R.: The Structural Changes of the Liver in Pernicious Anemia, Arch. Path. **8**:213, 1929.

Meyer-Betz, F.: Die Lehre vom Urobilin, Ergebn. d. inn. Med. u. Kinderh. **12**: 733, 1913.

Mueller, F.: Ueber Icterus, Jahresb. d. Schlesische Gesellsch. f. vaterl. Cult., Breslau, Med. Sect., 1892, pp. 1-13.

Chronische Leberentzündung (Discussion), Verhandl. d. kong. f. inn. Med. **11**: 118, 1892.

Nencki, M., and Zaleski, J.: Ueber Reduktions Produkte des Hämins durch Jodwasserstoff und Phosphonium Jodid und ueber die Constitution des Hämins und seiner Derivate, Ber. d. deutsche chem. Gesellsch. **34**:997, 1901.

Neubauer, O.: Bedeutung der Ehrlichschen Farben reaktion, München. med. Wchnschr. **50**:1846, 1903.

Opitz, H., and Choremis, K.: Untersuchungen ueber den Urobilinstoffwechsel bei Kindern, insbesondere nach Bluttransfusionen, und im Tierversuch, Jahrb. f. Kinderh. **115**:23, 1927.

Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests: A Comparative Study, J. A. M. A. **91**:1768 (Dec. 8) 1928.

Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts, as Applied to the Common Duct, J. Exper. Med. **37**:11, 1923.

Royer, M.: Dosage de l'urobiline, Compt. rend. Soc. de biol. **99**:1003, 1928.

Urobiline des organes, ibid. **99**:1006, 1928.

Saillet: De la urobiline dans les urines normal, Rev. de méd. **17**:109, 1897.

Schulten, H.: Wo greift die Lebertherapie der perniziösen an? München. med. Wchnschr. **75**:633, 1928.

Simpson, G. C. E.: On the Quantitative Estimation of Urobilin in the Excreta, and Its Value as a Measure of Haemoglobin Metabolism, Biochem. J. **6**:378, 1911.

Terwen, A. J. L.: Ueber ein neue Verfahren zur quantitative Urobilin Bestimmung im Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:72, 1925.

Van Lair and Masius: Ueber einen neuen Abkommling des Gallenfarbstoffes im Darminhalt, Centralbl. f. d. med. Wissensch., 1871, pp. 369-371.

Wallace, C. B., and Diamond, J. S.: Significance of Urobilogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:689 (June) 1925.

Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

CENTRAL VASOMOTOR IRRITABILITY

CONTRIBUTION TO THE PROBLEM OF ESSENTIAL HYPERTENSION *

W. RAAB, M.D.
Rockefeller Research Fellow
VIENNA, AUSTRIA

In a previous paper [1] there was described a characteristic feature of essential (not nephritic) hypertension, namely, an increased sensitivity of the vasomotor centers to changes in alveolar carbon dioxide tension: abnormally high rises of blood pressure during the inhalation of carbon dioxide and an abnormal fall of blood pressure during the increased exhalation of carbon dioxide (hyperventilation; Tirala [2] and Rappaport [3]). There is a striking parallelism between the figures of alveolar carbon dioxide and of blood pressure during hyperventilation in hypertonic patients, while a fall of carbon dioxide to the same extent does not change the blood pressure of hyperventilating normal persons in any definite way (Collin, Densham and Wells,[4] Schneider [5]). From this characteristically different behavior of normal and hypertonic persons the conclusion has been drawn that a pathologic hypersensitivity of the vasomotor centers (not only to abnormally high amounts of carbon dioxide but even to the normal carbon dioxide content of the blood) may be an important factor contributing to the high blood pressure level in hypertonic persons. Carbon dioxide acts, as is well known, as a specific stimulant on the central vasomotor apparatus. Henderson [6] said: "Carbon dioxide tension in the nerve centers . . . is a factor in the maintenance of tonus." Furthermore, it has recently been shown by Weiss and Ellis [7] that the increased blood pressure in hypertension is due to a contraction of the peripheral vessel system and not to primary changes in the general blood volume, cardiac output,

* Submitted for publication, June 13, 1930.

* From the Department of Physiology, Harvard Medical School, Boston.

1. Raab, W.: Ztschr. f. d. ges. exper. Med. **68**:337, 1929.
2. Tirala, L.: Wien. klin. Wchnschr. **5**:137, 1929.
3. Rappaport, Israel: Blood Pressure and Respiration: Hyperventilation as a Treatment for Hypertension, J. A. M. A. **92**:1158 (April 6) 1929.
4. Collin, Densham and Wells: Quart. J. Exper. Physiol. **18**:291, 1927.
5. Schneider, E. C.: Am. J. Physiol. **91**:390, 1930.
6. Henderson, Y.: Am. J. Physiol. **24**:66, 1909.
7. Weiss and Ellis: Am. Heart J. **5**:635 (June) 1930.

circulation through the lungs or velocity of the blood flow. This also suggests a dominant rôle of the vasomotor centers in hypertension.

The question arose, What is the cause of that hyperirritability, and by what means would it be possible to imitate similar conditions experimentally in animals? Many outstanding investigators attribute an essential importance for the genesis of hypertension to central nervous factors (von Monakow,[8] Krehl,[9] Pal,[10] Goldscheider,[11] Kahler,[12] A. Loewy,[13] Cobet,[14] etc.). Emphasis has been put on the frequent presence of arteriosclerotic alterations of the vessels of the brain (Riebold,[15] Lippmann[16] Munk[10] and others). A thorough histologic study of the latter subject has recently been published by Bordley and Baker[17] concerning twenty-four cases of arteriosclerosis, in fourteen of which the patients had suffered from doubtless hypertension while in ten the blood pressure had been normal. The authors found sclerotic alterations in the walls of the vessels of the medulla oblongata in the hypertonic patients but not in those with normal blood pressure. It is true that Cutler[18] observed conditions of the kind mentioned in only about 25 per cent of eighteen brains from hypertonic persons, but on the other hand the possibility of spastic contractions even of the vessels of the brain not leaving any anatomic traces has frequently been emphasized. Finally, it may be mentioned that a rise in blood pressure can also be caused by an increase of intracranial pressure (Cushing,[19] Kahler[12] and others). All investigators unanimously assume the diminishing of the supply of blood and oxygen to be the essential moment in the importance of all of the different conditions for the increased tonus of the vasomotor centers. Experimental evidence for this conception has been given by Mathison[20] and Anrep and Starling,[21]

---

8. von Monakow, P.: Deutsches Arch. f. klin. Med. **115**:47 and 224, 1914; **133**:1983, 1920.

9. Krehl, in von Mering, J.: Lehrbuch der inneren Medizin, ed. 13, Jena, Gustav Fischer, 1921.

10. Quoted by Kahler: Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1924.

11. Goldscheider: Ztschr. f. phys. u. diätet. Therap. **23**:25, 1919; **25**:1, 1921.

12. Kahler: Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1914.

13. Loewy, A.: Arch. f. d. ges. Physiol. **207**:632, 1925.

14. Cobet: Biochem. Ztschr. **137**:67, 1923.

15. Riebold: München. med. Wchnschr., 1917, vol. 43.

16. Lippmann: Deutsche med. Wchnschr. **44**:907, 1918.

17. Bordley, J. III, and Baker, B. M., Jr.: Bull. Johns Hopkins Hosp. **38**:320, 1926; **39**:229, 1926.

18. Cutler, O. I.: Relation of Arteriosclerosis of Cerebral Vessels to Hypertension: Distribution of Arteries Supplying the Pons and Medulla, Arch. Path. **5**:365 (March) 1928.

19. Cushing: Bull. Johns Hopkins Hosp. **12**:290, 1901.

20. Mathison: J. Physiol. **41**:416, 1910; **42**:283, 1911.

21. Anrep and Starling: Proc. Roy. Soc. Med. **97**:463, 1924.

as well through artificial reduction of the circulation of the brain, as by cutting down the respiratory oxygen supply; furthermore, Gurdjian [22] produced strong increases of blood pressure by the application of sodium cyanide to the medulla oblongata, which prevents oxidation.

Lack of oxygen causes an accumulation of lactic acid not only in the muscles (Fletcher and Hopkins,[23] etc.) but also in the nervous (Fenn,[24] Gerard [25]) and brain tissue (McGinty and Gesell,[26] Cobet [27]) especially in the medulla oblongata (Haldi, Ward and Woo [28]). On the other hand it is known that acids generally stimulate the vasomotor centers (Traube,[29] Mathison,[30] Bainbridge,[30] Itami,[31] Cobet,[14] Eppinger, Kisch and Schwarz,[32] Gesell,[33] Gollwitzer-Meier [34] and others). In regard to those facts it is not too far fetched to imagine that even the clinical hypertonic blood pressure might be at least partly due to an accumulation of acid substances, especially of lactic acid within the region of the vasomotor centers as a consequence of local circulatory disturbance and thus a diminished oxygen supply, an idea that has already been suggested by Cobet,[14] Lichtwitz [35] and A. Loewy.[13] (Straub and Meier [36] and von Romberg [37] have applied the same conception to the respiratory center for explaining "central dyspnea.")

This hypothesis being logically well enough founded, it seemed worth while to search for experimental evidence. It was considered as a suitable procedure in this direction to examine the effect of a diminished supply of oxygen and of artificial acidification of the centers concerning not only the sufficiently well studied plain rise of blood pressure but mainly the degree of irritability under those conditions. In other words, Do the shortage of oxygen and the presence of lactic acid in the vaso-

22. Gurdjian, E. S.: Am. J. Physiol. **82**:261, 1927.
23. Fletcher and Hopkins: J. Physiol. **35**:247, 1907.
24. Fenn, W. O.: Am. J. Physiol. **80**:327, 1927.
25. Gerard, R. W.: Am. J. Physiol. **82**:381, 1927.
26. McGinty, D. A., and Gesell, R.: Am. J. Physiol. **83**:323, 1927.
27. Cobet: Arch. f. exper. Path. u. Pharmakol. **145**:140, 1929.
28. Haldi, J. A.; Ward, H. P., and Woo, L.: Am. J. Physiol. **83**:250, 1927.
29. Traube: Gesammelte Abhandlungen, Berlin, A. Hirschwald, 1856, vol. 2.
30. Bainbridge, F. A.: J. Physiol. **54**:192, 1920-1921.
31. Itami: J. Physiol. **45**:338, 1912-1913.
32. Eppinger, Kisch and Schwarz: Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927.
33. Gesell, R.: Ergebn. d. Physiol. **28**:340, 1929.
34. Gollwitzer-Meier, K.: Arch. f. d. ges. Physiol. **222**:104 and 124, 1929.
35. Lichtwitz: Die Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1925; quoted by Blum, R.: Ergebn. d. inn. Med. u. Kinderh. **35**:255, 1929.
36. Straub, H., and Meier, K.: Deutsches Arch. f. klin. Med. **138**:208, 1922.
37. von Romberg, E.: Wien. med. Wchnschr. **80**:361, 1930.

motor centers produce besides an irritation of the centers an increased irritability which is an important characteristic of essential hypertension? Evidence for hyperirritability in hypertonic men has been given by the reactions to changes of alveolar (blood) carbon dioxide, as mentioned, and by the sudden abnormally high rises of blood pressure due to peripheral stimuli, especially to pain (Curschmann,[10] Pal,[38] Kahler,[12] Eisenfarb[39] and others) and to psychic emotions (Külbs,[40] Ayman[41] and others).

A general increase of nervous excitability under the influence of a shortage of oxygen and under the action of acids has been reported by various authors (Bethe,[42] Syz,[43] Boehm,[44] Batelli,[45] Elias,[46] Winterstein,[47] Kaya and Starling,[48] Brailsford-Robertson[49] and others). Haldane and his collaborators[50] observed an increased sensitivity of the respiratory center to carbon dioxide through the diminution of oxygen. Gesell[33] assumed that the respiratory center is more sensitive to carbon dioxide the less it is buffered. Cobet[51] and Mosler[52] observed a stronger increase of blood pressure in hypertonic than in normal persons if the supply of oxygen was cut down. Mathison[20] found a summation of the effects of the infusion of acids and the inhalation of carbon dioxide in decerebrate cats. He also discussed the possibility that the lack of oxygen caused an "intraneural" formation of acids in an amount sufficiently high to excite the vasomotor centers but not to be detected in the circulating blood.

The fact that painful peripheral stimuli cause a rise in blood pressure has been stated by Heidenhain,[53] Bradford,[10] Tigerstedt[10] and others.

---

38. Pal, J.: Die Gefässkrisen, Leipzig, S. Hirzel, 1905; footnote 10.
39. Eisenfarb, J.: Klin. Wchnschr. **9**:552, 1930.
40. Külbs, in Mohr-Staehelin: Lehrbuch der inneren Medizin, ed. 2, Munich, J. F. Bergmann, vol. 2, p. 443.
41. Ayman, D.: Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94**:1214 (April 19) 1930.
42. Bethe: Ergebn. d. Physiol. **5**:250, 1906.
43. Syz: J. Pharmacol. **30**:1, 1907.
44. Boehm: Arch. f. exper. Path. u. Pharmakol. **8**:68, 1878.
45. Batelli: J. de physiol. et de path. gén. **2**:443, 1900.
46. Elias: Ergebn. d. inn. Med. u. Kinderh. **25**:192, 1924.
47. Winterstein: Ztschr. f. allg. Physiol. **3**:359, 1903.
48. Kaya and Starling: J. Physiol. **39**:346, 1909-1910.
49. Brailsford-Robertson: Festschrift für Hamburger, 1905, p. 287; quoted by Elias (footnote 46).
50. Haldane and Poulton: J. Physiol. **37**:390, 1908. Haldane and Boycott: J. Physiol. **37**:369, 1908. Douglas and Haldane: J. Physiol. **38**:420, 1909.
51. Cobet: Deutsches Arch. f. klin. Med. **143**:253, 1924.
52. Mosler: Ztschr. f. klin. Med. **78**:133, 1913.
53. Heidenhain: Arch. f. d. ges. Physiol. **3**:505, 1870; **5**:77, 1872.

It is usually considered as being a reflex phenomenon, although even a discharge of epinephrine from the suprarenals can play a rôle under certain conditions (Cannon,[54] Houssay and Molinelli,[55] Tournade and Chabrol,[56] and others.)

In the following experiments inhalation of carbon dioxide, hyperventilation and electric stimulation of the crural nerve have been used as tests for the excitability of the vasomotor centers under various conditions.

Finally, there exists a rather characteristic feature in essential hypertension in man—a frequently reverted or at least weakened response of the blood pressure to epinephrine (Schlesinger and Arnstein,[57] Dresel,[58] Jansen,[59] Kaufmann,[60] Kylin,[61] Basch[60] and others). Intravenous injections of epinephrine have therefore also been used as a test for experimental hypertonic conditions.

TECHNIC

In all of the experiments, cats decerebrated under ether anesthesia have been used because the reactivity of the vasomotor centers had been found to be too much injured by continuous anesthesia (von Esveld[62]). The vagi on the left and the right sides were cut.

Registration of the blood pressure was done with a mercury manometer partly from the femoral artery and partly from the left carotid artery. Graphical registration was taken of the intratracheal air pressure.

Lactic acid and other substances were injected through a cannula tied into the central stump of the right carotid artery and connected with the syringe by means of a thick rubber tubing. By this method the liquid injected reaches the brain stem through the right vertebral artery. Longer lasting infusions were made with a special apparatus designed by Dr. Magnus Gregersen, to be described subsequently by himself—an electrically driven pinion mechanism which warrants a regular pushing forward of the piston of the fixed syringe with various definite slow speeds.

The control analyses of the gas mixtures were made by Miss E. Bright. A spirometer was inserted between the steel tanks and the respiration valves.

For artificial respiration, an air pump constructed by Prof. C. Drinker was used. Its speed could be varied between fifteen and twenty-six revolutions per minute, the single stroke volume being between 0 and 97 cc.

---

54. Cannon: Am. J. Physiol. **1**:399, 1919.
55. Houssay, B. A., and Molinelli, E. A.: Rev. Soc. argent. de biol. **1**:125, 1925.
56. Tournade, A., and Chabrol, M.: Compt. rend. Soc. de biol. **92**:418, 1925.
57. Schlesinger and Arnstein: Wien. klin. Wchnschr. **49**:1179, 1919.
58. Dresel: Deutsche med. Wchnschr. **45**:955, 1919.
59. Jansen, W. H.: Deutsches Arch. f. klin. Med. **147**:339, 1925.
60. Quoted by Kylin, Eskil: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.
61. Kylin, Eskil: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.
62. von Esveld: Arch. f. exper. Path. u. Pharmakol. **147**:297, 1930.

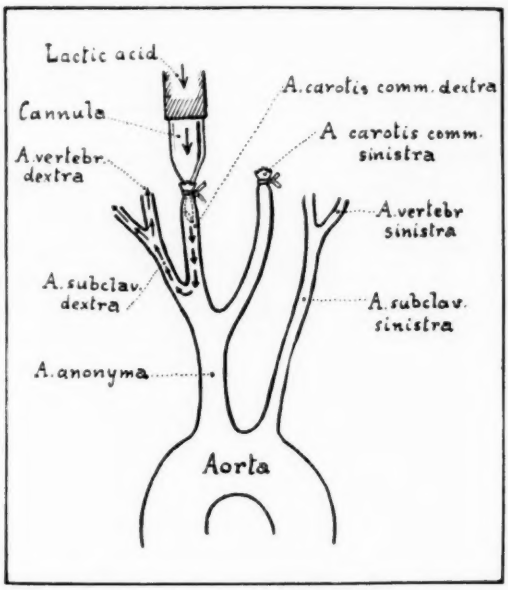

Fig. 1.—After Reighard and Turnings: The Anatomy of the Cat, New York, Henry Holt & Company, 1925.

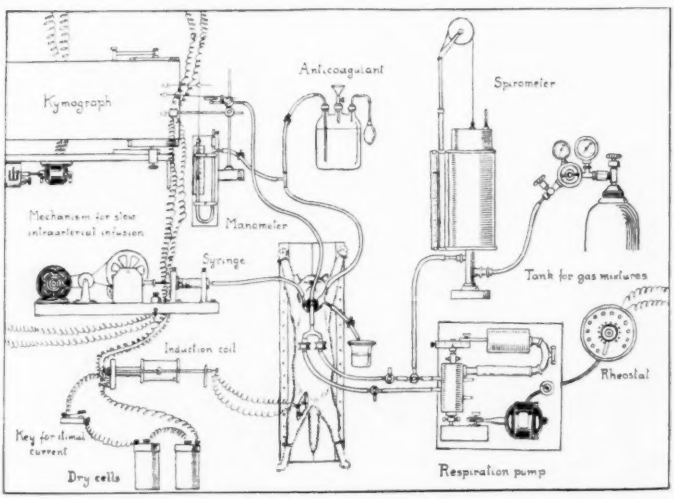

Fig. 2.—Apparatus used in the experiments.

The single periods of the experiments were generally separated by intervals of from ten to thirty minutes to secure sufficient recovery after each period.

The greater number of experiments were done with the maintenance of the spontaneous respiration, because a poisoning with curare is not quite indifferent for the mode of reaction of the vasomotor centers (Grützner and Heidenhain,[63] Latschenberger and Deahna,[64] Tillie,[65] Martin and Stiles[66]), while without paralysis of the breathing muscles, disturbing interferences occur between spontaneous and artificial respiratory movements of the chest.

TABLE 1.—*Effect of Carbon Dioxide Together with Want of Oxygen*

Experiment	Period of Experiment	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Oxygen, per Cent	Nitrogen, per Cent	Duration of Experimental Period, Minutes	Blood Pressure: Initial	Maximum Attained	Deviation	Comparison of Results
1	a	3.6	25	71.4	2	96	115	+19	b = a + c + 11
	b	3.6	10	86.4	2	94	120	+26	
	c	...	10	90.0	2	100	106	+ 6	
2	a	6.0	25	69.0	2	124	146	+22	c = a + b - 5
	b	...	10	90.0	2	96	106	+10	
	c	6.0	10	84.0	2	94	131	+37	
3	a	...	10	90.0	2	110	116	+ 6	c = a + b + 4
	b	6.0	25	69.0	2	120	152	+32	
	c	6.0	10	84.0	2	96	138	+42	
4	a	6.0	25	69.0	2	98	86	−12	c = a + b + 33
	b	...	10	90.0	2	92	96	+ 4	
	c	6.0	10	84.0	2	96	121	+25	
5	a	6.0	25	69.0	2	118	211	+93	c = a + b + 10
	b	...	10	90.0	2	112	139	+27	
	c	6.0	10	84.0	2	102	232	+130	
6	a	3.6	25	71.4	2	164	182	+18	b = a + c + 6
	b	3.6	10	86.4	2	162	194	+34	
	c	...	10	90.0	2	160	170	+10	
7	a	...	10	90.0	2	132	147	+15	c = a + b + 20
	b	3.6	25	71.4	2	116	136	+20	
	c	3.6	10	86.4	2	70	164	+94	

EXPERIMENTS

Combination of Effect of Carbon Dioxide with Want of Oxygen (table 1).—These experiments show without exception an increase of the effect of carbon dioxide on blood pressure if combined with a diminished supply of oxygen: The effect of carbon dioxide with only 10 per cent of oxygen gives a higher rise in blood pressure than the sum of the single effects of carbon dioxide alone and of 10 per cent of oxygen alone.

63. Grützner and Heidenhain: Arch. f. d. ges. Physiol. **16**:47, 1878.

64. Latschenberger and Deahna: Arch. f. d. ges. Physiol. **12**:157, 1876.

65. Tillie, quoted by Boehm: Handbuch der experimentellen Pharmakologie, Berlin, A. Heffter, 1920, vol. 2, p. 179.

66. Martin and Stiles: Am. J. Physiol. **34**:220, 1914.

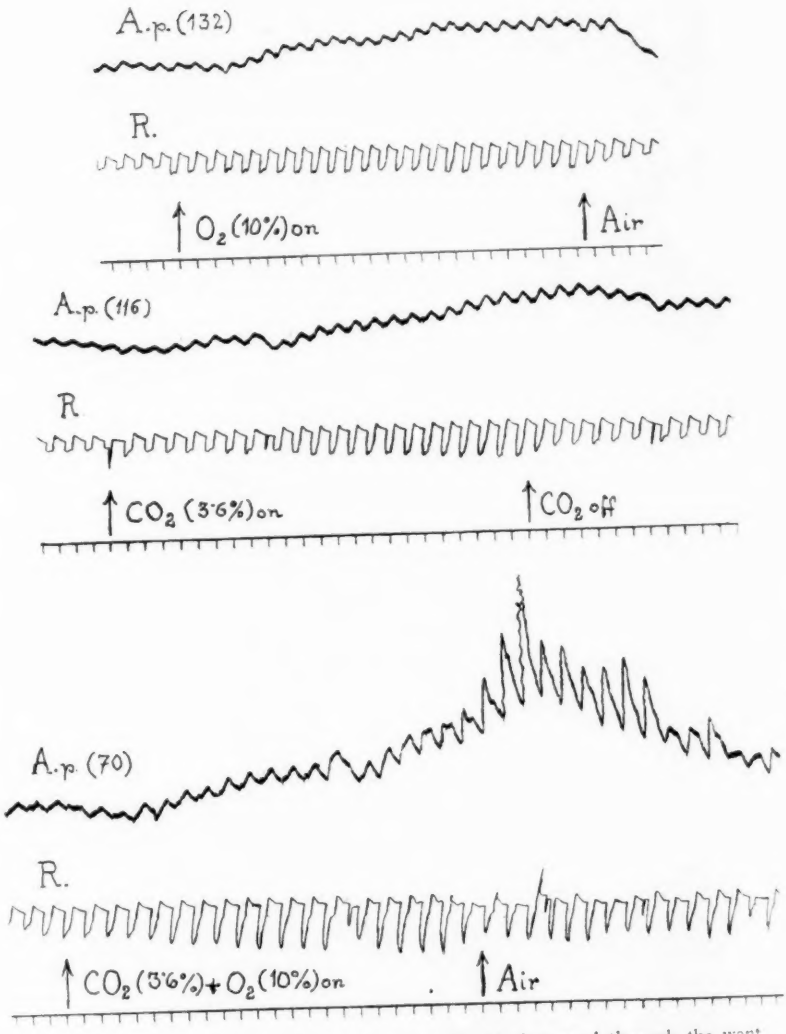

Fig. 3 (experiment 7).—Effect of carbon dioxide increased through the want of oxygen.

Combination of Effect of Carbon Dioxide with Lactic Acid (tables 2 and 3).—As it had been planned to inject diluted lactic acid into the right carotid artery, one had to reckon with the theoretical possibility that the mere dilution of the blood (although being very moderate) could

TABLE 2.—*Controls with Saline Solution Injected into the Central Stump of the Right Carotid and the Effect of Carbon Dioxide*

Experiment	Period of Experiment	Sodium Chloride Infused: Concentration, per Cent	Sodium Chloride Infused: Volume, Cc.	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Experimental Period, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
8	a	...	..	3	25	72	2	150	171	+21	a = b
	b	0.9	3	3	25	72	2	154	175	+21	

TABLE 3.—*Lactic Acid Injected into the Central Stump of the Right Carotid and the Effect of Carbon Dioxide*

Experiment	Period of Experiment	Lactic Acid Infused: Concentration, per Cent	Lactic Acid Infused: Volume, Cc.	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Experimental Period, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
9	a	.....	...	3.6	25	71.4	2	120	147	+27	c = a + b + 24
	b	n/20	3.0	...	Air	....	2	112	129	+17	
	c	n/20	3.0	3.6	25	71.4	2	118	186	+68	
10	a	.....	...	3.6	25	71.4	2	140	178	+38	c = a (respectively
	b	n/20	2.5	...	Air	....	2	104	104	± 0	
	c	n/20	2.5	3.6	25	71.4	2	72	138	+66	d) + b + 28
	d	.....	...	3.6	25	71.4	2	46	84	+38	
11	a	.....	...	6.0	25	69.0	2	132	171	+39	c = a + b + 7
	b	n/20	3.0	...	Air	....	2	110	130	+20	d = a + b + 18
	c	n/20	3.0	6.0	25	69.0	2	136	202	+66	
	d	n/20	3.0	6.0	25	69.0	2	120	197	+77	
	e	.....	...	6.0	25	69.0	2	136	166	+37	
12	a	.....	...	6.0	25	69.0	2	124	146	+22	b = a + c + 64
	b	n/20	3.0	6.0	25	69.0	2	90	179	+89	d = a + c + 6
	c	n/20	3.0	...	Air	....	2	90	93	+ 3	
	d	n/20	...	6.0	25	69.0	2	96	125	+31	
13	a	.....	...	3.0	25	72.0	2	114	132	+18	c (150″
	b	n/20	3.0	...	Air	....	2	108	135	+27	after b) =
	c	n/20	(3.0)	3.0	25	72.0	2 (6)	135(108)	166	+58	a + b + 13
14	a	.....	...	3.0	25	72.0	2	150	155	+ 5	c = a + b + 11
	b	n/20	2.0	...	Air	....	2	136	148	+12	
	c	n/20	2.0	3.0	25	72.0	2	106	134	+28	
15	a	.....	...	3.6	25	71.4	2	74	95	+21	c = a + b + 27
	b	n/15	2.0	...	Air	....	2	60	76	+16	
	c	n/15	2.0	3.6	25	71.4	2	64	128	+64	

perhaps affect the tonus of the vasomotor centers in consequence of the somewhat diminished oxygen content of the diluted blood. This is, however, not the case, as the control experiment 8 (table 2) shows.

In all of these experiments, the effect of carbon dioxide on the blood pressure was increased by the simultaneous (in experiment 13 by previous) injection of lactic acid into the central stump of the right carotid

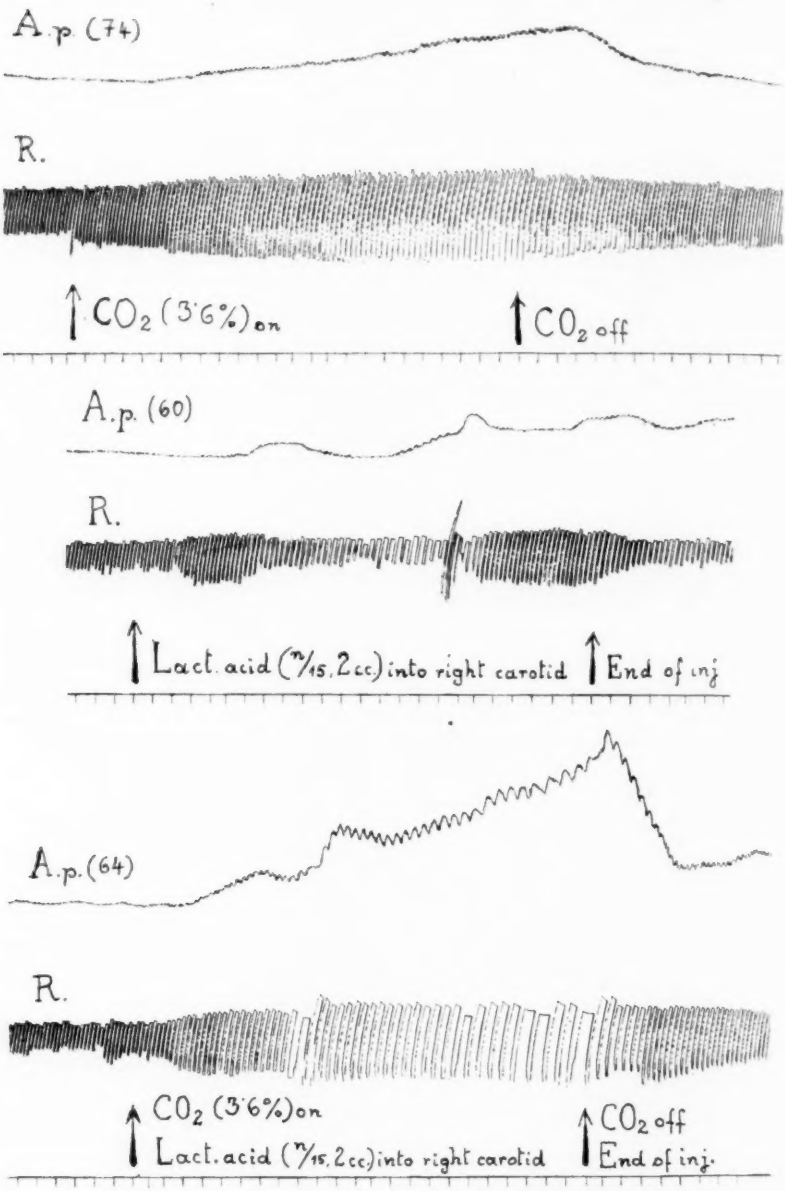

Fig. 4 (experiment 15).—Effect of carbon dioxide increased through the infusion of lactic acid.

artery. The effect of lactic acid and carbon dioxide combined is considerably higher than the sum of the single effects.

Combination of Effect of Carbon Dioxide with Acetic Acid (table 4).—Although acetic acid in the concentration used (twentieth-normal) does not cause an increase but rather a slight decrease of blood pressure, the effect of carbon dioxide in its presence is still intensified.

Effect of Carbon Dioxide After Injection of Lactic Acid into the Suboccipital Cavity (tables 5 and 6).—In the following experiments, after having exposed the atlanto-occipital membrane, lactic acid (and as a control physiologic solution of sodium chloride) was injected into the cerebrospinal cavity not far from the region of the vasomotor

TABLE 4.—*Acetic Acid Injected into the Central Stump of the Right Carotid and Effect of Carbon Dioxide*

Experiment	Period of Experiment	Acetic Acid Infused: Concentration, per Cent	Acetic Acid Infused: Volume, Cc.	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Experimental Period, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
16	a	.....	..	3	25	72	2	150	155	+ 5	c = a + b + 19
	b	n/20	2	..	Air	..	2	150	136	—14	
	c	n/20	2	3	25	72	2	146	156	+10	
17	a	n/20	3	..	Air	..	2	90	86	— 4	c = a + b + 8
	b	.....	..	6	25	69	2	120	152	+32	
	c	n/20	3	6	25	69	2	114	150	+36	
18	a	.....	..	3	25	72	2	120	121	+ 1	c = a + b + 33
	b	n/20	3	..	Air	..	2	90	86	— 4	
	c	n/20	3	3	25	72	2	90	120	+30	

centers. To avoid an undesired rise of pressure within the cerebrospinal cavity, an amount of liquor was first allowed to escape through the puncture hole. The amount of fluid injected that remained inside the dura is not exactly known because a part of it escaped after removal of the needle; it might be roughly estimated as about 0.5 cc. of each of the fluids injected. The control experiment (19, table 5) showed a slightly diminished effect of carbon dioxide after the injection of salt solution. After the injection of the lactic acid, on the contrary, the effect of carbon dioxide was considerably intensified within a space of time, from one to twenty minutes after the injection. (In experiment 20, the injection of the lactic acid itself caused a short-lasting fall of blood pressure of 16 mm.; in the other experiments, short-lasting rises of 62, 13 and 57 mm., with a following return below the initial level. The injection of salt solution did not alter the blood pressure.)

Combination of Effect of Carbon Dioxide with Sodium Carbonate (table 7).—The results of these experiments are irregular concerning both the action of sodium carbonate itself and its influence on the effect

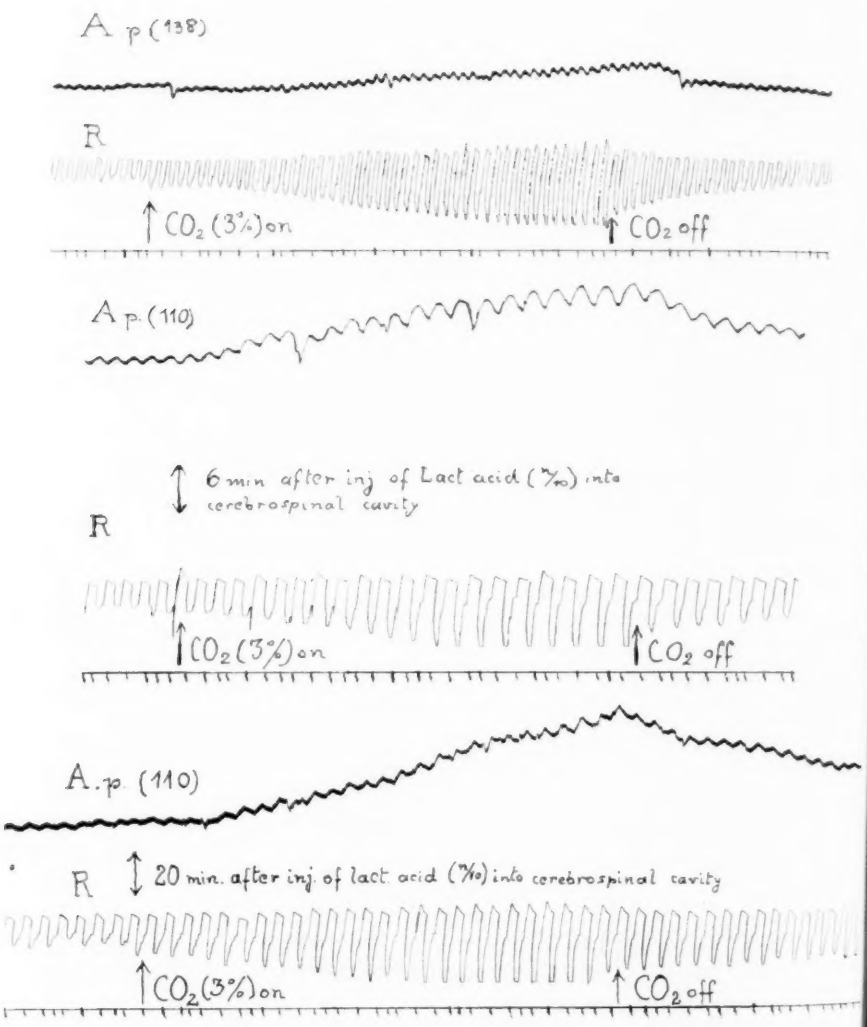

Fig. 5 (experiment 22).—Effect of carbon dioxide increased through the infusion of lactic acid into the cerebrospinal cavity.

TABLE 5.—*Control with Saline Solution Injected into the Suboccipital Cavity and Effect of Carbon Dioxide*

Experiment	Period of Experiment	Sodium Chloride Injected: Concentration, per Cent	Sodium Chloride Injected: Volume, Cc.	Onset of Inhalation of Carbon Dioxide, Minutes After Injection	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Inhalation, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
19	a	....	..	..	3.6	25	71.4	2	74	95	+21	b = a—8
	b	0.9	cca. 0.5	1	3.6	25	71.4	2	76	89	+13	

TABLE 6.—*Effect of Carbon Dioxide After Injection of Lactic Acid into the Suboccipital Cavity*

Experiment	Period of Experiment	Lactic Acid Injected: Concentration, per Cent	Lactic Acid Injected: Volume, Cc.	Onset of Inhalation of Carbon Dioxide, Minutes After Injection	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Inhalation, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
20	a	..	..	..	3.6	25	71.4	2	74	95	+21	c = a+9
	b	2	cca. 0.5	3	3.6	25	71.4	2	68	98	+30	
21	a	..	..	..	3.6	25	71.4	2	120	140	+20	c = a+6
	b	1	cca. 0.5	5	3.6	25	71.4	2	107	133	+26	d = a+16
	c			20	3.6	25	71.4	2	102	138	+36	
22	a	..	..	..	3.0	25	72.0	2	138	148	+10	c = a+20
	b	1	cca. 0.5	6	3.0	25	72.0	2	110	140	+30	d = a+36
	c			20	3.0	25	72.0	2	110	156	+46	
23	a	..	..	..	3.6	25	71.4	2	120	145	+25	c = a+83
	b	3	cca. 0.5	1	3.6	25	71.4	2	76	184	+108	

TABLE 7.—*Sodium Carbonate Injected into the Central Stump of the Right Carotid and Effect of Carbon Dioxide*

Experiment	Period of Experiment	Sodium Carbonate Injected: Concentration, per Cent	Sodium Carbonate Injected: Volume, Cc.	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Experimental Period, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
24	a	.....	..	6	25	69	2	134	164	+30	b = a+c+32
	b	n/10	3	6	25	69	2	116	190	+74	e = d+f+14
	c	n/10	3	..	Air	..	2	118	130	+12	g = d+f+20
	d	.....	..	6	25	69	2	110	145	+35	
	e	n/10	3	6	25	69	2	110	165	+55	
	f	n/10	3	..	Air	..	2	90	96	+ 6	
	g	n/10	3	6	25	69	2	96	157	+61	
25	a	.....	..	3	25	69	2	150	171	+21	b = a+c+5
	b	n/20	3	3	25	69	2	160	175	+15	
	c	n/20	3	..	Air	..	2	170	159	—11	
26	a	.....	..	3	25	69	2	150	171	+21	b = a+c—4
	b	n/10	3	3	25	69	2	160	183	+23	
	c	n/10	3	..	Air	..	2	170	176	+ 6	
27	a	n/20	3	..	Air	..	2	110	105	— 5	b = a+c—37
	b	n/20	3	6	25	69	2	116	96	—20	
	c	.....	..	6	25	69	2	90	112	+22	
28	a	.....	..	6	25	69	2	66	146	+80	c = a+b—44
	b	n/20	3	..	Air	..	2	64	89	+25	
	c	n/20	3	6	25	69	2	66	127	+61	
29	a	.....	..	6	25	69	2	66	146	+80	c = a+b—70
	b	n/10	3	..	Air	..	2	70	121	+51	
	c	n/10	3	6	25	69	2	70	131	+61	

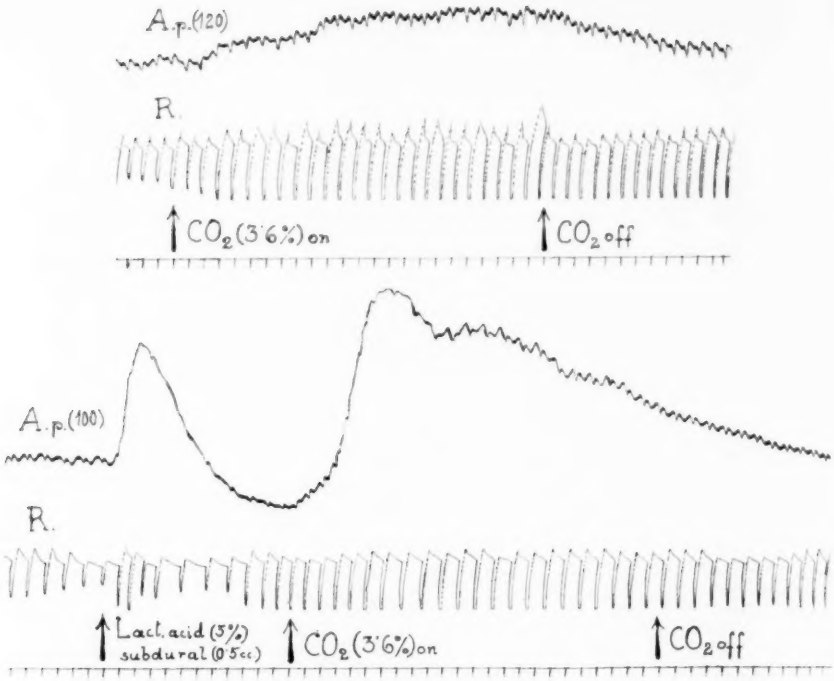

Fig. 6 (experiment 23).—Effect of carbon dioxide increased by lactic acid in the cerebrospinal cavity.

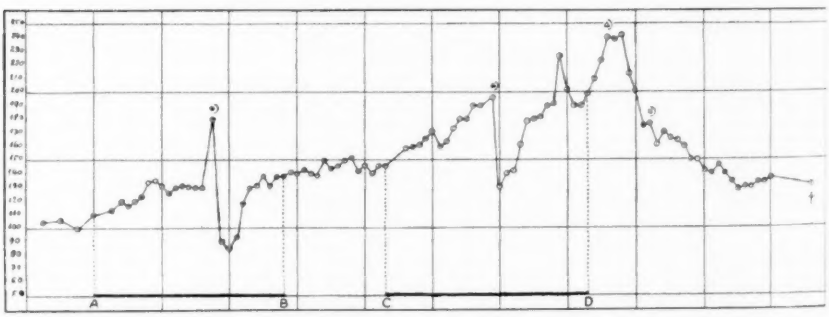

Fig. 7 (experiment 30).—The section between *A* and *B* indicates the infusion of lactic acid (2.5 per cent, 0.15 cc. per minute into the central stump of the right carotid artery during fifty-six minutes). The section between *B* and *C* indicates a thirty minute pause. The section between *C* and *D* indicates the infusion of lactic acid (5 per cent, 0.15 cc. per minute for sixty minutes). The asterisks indicate the points after the cannula had been washed out, and the femoral artery had been twitched. The triangle indicates the periods of apnea and cardiac arrhythmia. The square indicates the point at which the respiration and rhythm of the heart were again normal. The dagger shows the point at which the animal was killed. The large squares indicate twenty minutes.

of the carbon dioxide. The latter can be increased (experiments 24 and 25) or decreased (experiments 26, 28 and 29), or even transformed into an absolute fall of blood pressure (experiment 27).

Prolonged Increase of Blood Pressure by Continuous Perfusion of the Brain Stem with Lactic Acid.—A cannula was tied into the right carotid and connected with a syringe the piston of which was pushed forward in a definite slow speed by a motor and pinion mechanism. All of these experiments were started after the blood pressure level had kept fairly constant for at least fifteen minutes. The readings of blood pressure were mostly done every two minutes. The results in experiment 30 were as follows:

0- 15 minutes ..... Average blood pressure 105 mm.
15- 70 minutes Lactic acid (2½ per cent, 0.15 cc. per minute) into central stump of right carotid.... Average blood pressure 126 mm.
70-100 minutes .....Average blood pressure, 144 mm.
100-160 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 176 mm. (Maximum, 222)

After the infusion of lactic acid was stopped, the blood pressure continued to increase to 242 mm. (one hundred and seventy-second minute), and then fell gradually to 128 (two hundred and sixth minute). The animal was killed in the two hundred and thirtieth minute with a blood pressure of 132.

In both lactic acid periods the manometer cannula had to be washed out because of clotting. The manipulations on the artery were followed in both cases by a short rise and a considerable fall in blood pressure which was, however, compensated again within from fifteen to twenty minutes. The highest rise in blood pressure during infusion of lactic acid was 112 mm. above the original level. The frequency and depth of respiration were not markedly increased during the whole experiment. The results of experiment 31 are shown in the following tabulation.

0-15 minutes .....Average blood pressure 133 mm.
15-78 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 163 mm. (Maximum 198)
78-84 minutes .....Average blood pressure 162 mm.

Another infusion of lactic acid was attempted but the animal collapsed and died within the first ten minutes. The highest rise during the

first lactic acid period amounted to +64 mm. above the original level. The results in experiment 32 were as follows:

0- 20 minutes .....Average blood pressure 60 mm.
20- 76 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 85 mm. (Maximum 98)
76- 82 minutes .....Average blood pressure 103 mm.
82-114 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 105 mm. (Maximum 120)

From the one hundred and fourteenth minute on, convulsions started and the blood pressure fell slowly; the animal was killed in the one hundred and twenty-fourth minute with a blood pressure of 60. The highest rises in the first lactic acid period were to +38 mm., in the second, +60 mm. The results in experiment 33 were as follows:

0-15 minutes .....Average blood pressure 124 mm.
15-65 minutes Lactic acid (7½ per cent, 0.15 cc. per minute).....Average blood pressure 129 mm.
65-75 minutes .....Average blood pressure 129 mm.
75-90 minutes Lactic acid (15 per cent, 0.15 cc. per minute).....Average blood pressure 195 mm. (Maximum 260)

From the ninetieth minute on there occurred convulsions, rapid fall in blood pressure and death shortly thereafter. The highest rise during the second period was + 136 mm., while the first period with a lactic acid concentration only half as strong had been practically uneffective. The results of experiment 34 are given in the following tabulation.

0-15 minutes .....Average blood pressure 141 mm.
15-30 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 175 mm. (Maximum 188)

The highest rise was +47 mm. The results in experiment 35 were as follows:

0-15 minutes .....Average blood pressure 135 mm.
15-45 minutes Lactic acid (5 per cent, 0.15 cc. per minute).....Average blood pressure 155 mm. (Maximum 172)

After the fortieth minute convulsions occurred. The animal was killed at that time. The highest rise was +37 mm.

In these six experiments the blood pressure could be maintained on an artificially increased level during a period varying from a quarter of an hour to two hours through the infusion of lactic acid. The intensity of response was individually different.

Effect of Carbon Dioxide During Continuous Infusion of Lactic Acid (table 8).—The effect of carbon dioxide on the blood pressure is also increased during continuous infusion of lactic acid, starting from an elevated blood pressure level.

TABLE 8.—*Continuous Infusion of Lactic Acid and Effect of Carbon Dioxide*

Experiment	Period of Experiment	Lactic Acid Infused: Concentration, per Cent	Lactic Acid Infused: Volume, Cc. per Minute	Lactic Acid Infused: Duration, Min.	Gas Mixture Inhaled: Carbon Dioxide, per Cent	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Duration of Experimental Period, Min.	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
36	a	...	....	..	3.5	25	71.5	2	106	122	+16	
	b	2.5	0.15	30	3.5	25	71.5	2	130	152	+22	b = a+6
	c	2.5	0.15	50	3.5	25	71.5	2	138	159	+21	c = a+5
	d	5.0	0.15	30	3.5	25	71.5	2	190	197	+ 7	d = a−9
37	a	...	....	..	3.5	25	71.5	2	128	159	+31	
	b	7.5	0.15	45	3.5	25	71.5	2	130	185	+55	b = a+24
38	a	...	....	..	3.5	25	71.5	2	124	148	+24	
	b	7.5	0.15	20	3.5	25	71.5	2	180	206	+26	b = a+2
39	a	...	....	..	3.5	25	71.5	2	130	162	+32	
	b	5.0	0.15	15	3.5	25	71.5	2	180	234	+54	b = a+22

TABLE 9.—*Hyperventilation Before and During Infusion of Lactic Acid*

Experiment	Period of Experiment	Lactic Acid Infused: Concentration, per Cent	Lactic Acid Infused: Volume, Cc. per Minute	Lactic Acid Infused: Duration, Minutes	Standard Respiration per Minute: Number of Respirations	Standard Respiration per Minute: Stroke Volume	Hyperventilation: Respirations per Minute	Hyperventilation: Stroke Volume	Hyperventilation: Increase, per Cent	Hyperventilation: Duration, Minutes	Average Blood Pressure: Before Hyperventilation	Average Blood Pressure: During Hyperventilation	Average Blood Pressure: After Hyperventilation (Within Sec.)	Deviation of Blood Pressure During Hyperventilation: Average	Deviation of Blood Pressure During Hyperventilation: Maximum
40	a	...	....	..	20	49	26	61	62	5	121	107	109 (50)	−14	−21
	b	5.0	0.07	30	20	49	26	61	62	5	159	128	148 (150)	−31	−39
41	a	...	....	..	20	49	26	61	62	5	60	60	73 (75)	± 0	− 4
	b	5.0	0.07	10	20	49	26	61	62	5	105	93	90 (50)	−12	−21
42	a	...	....	..	20	55	26	67	58	5	113	104	104 (50)	− 9	−15
	b	5.0	0.07	12	20	55	26	67	58	5	162	140	150 (130)	−22	−34
43	a	...	....	..	20	61	26	79	68	5	118	111	111 (75)	− 7	−12
	b	7.5	0.15	10	20	61	26	79	68	5	147	122	131 (150)	−25	−41
	c	7.5	0.07	26	20	61	26	79	68	5	178	164	156 (100)	−14	−32
	d	7.5	0.07	45	20	61	26	79	68	5	183	173	173 (100)	−10	−18
44	a	...	....	..	26	55	26	69	26	5	110	130	149 (100)	+20	+38
	b	...	....	..	26	55	26	73	33	5	116	145	174 (40)	+29	+50
	c	5.0	0.15	6	26	55	26	69	26	5	130	130	139 (80)	± 0	−6, +10
	d	5.0	0.15	20	26	55	26	73	33	5	128	123	123 (60)	− 5	−8, +2
45	a	...	....	..	26	55	26	73	33	5	60	99	119 (60)	+39	+52
	b	5.0	0.15	10	26	55	26	73	33	5	73	73	88 (60)	± 0	−8, +14

Effect of Hyperventilation Before and During Continuous Infusion of Lactic Acid (table 9).—These experiments were particularly difficult to do because of the irregularities in blood pressure caused by curare, which had to be used for maintaining a regular artificial respiration. Suitable constant conditions for periods of from eight to ten minutes as needed for this kind of experiment were only rarely available. Artificial hyperventilation was done in a very moderate degree for

excluding mechanical factors as far as possible. At each change of respiration rate the air pump had to be stopped for a few seconds, which usually caused a short-lasting slight asphyctic rise in blood pressure, but did not otherwise influence the conditions. The figures in

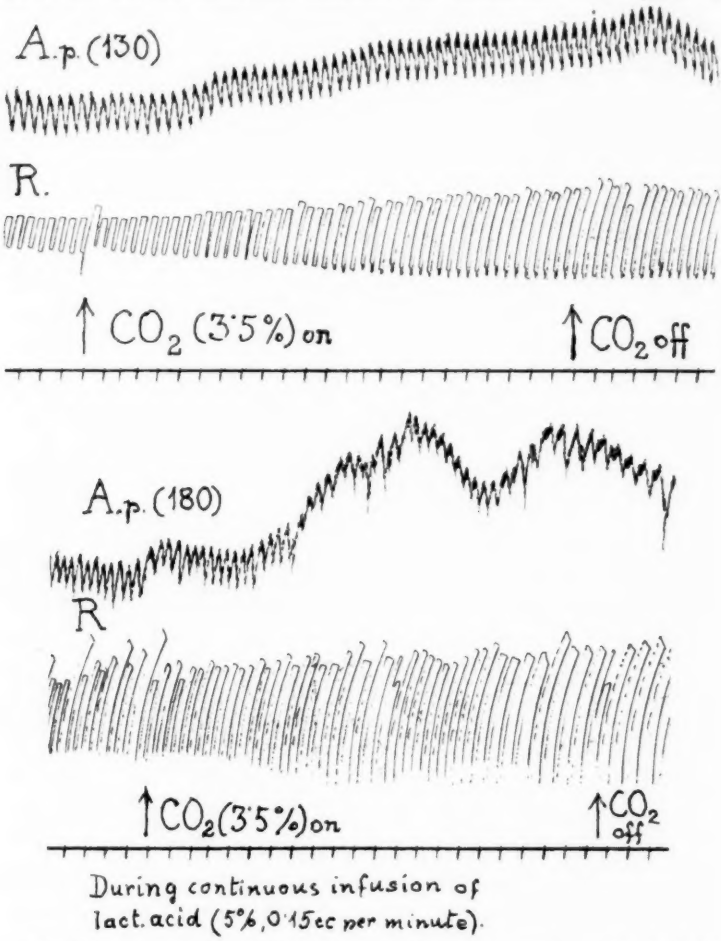

Fig. 8 (experiment 39).—Effect of carbon dioxide increased through the infusion of lactic acid.

table 9 are averages of blood pressure values measured on the diagrams at intervals of from twenty-five to thirty seconds. When definite waves in blood pressure occurred (experiment 40), only the tops of the waves were taken into consideration.

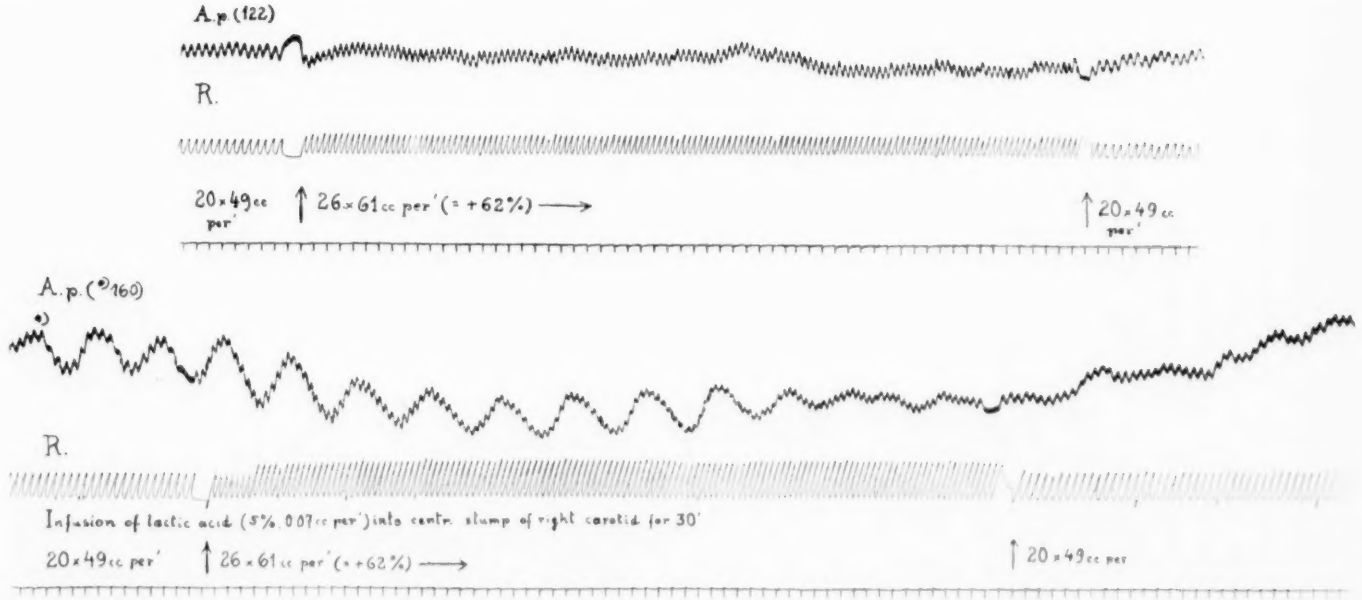

Fig. 9 (experiment 40).—Effect of hyperventilation increased by the infusion of actic acid. (The size of the respiratory movements appears different in the first and second part of the experiment on account of a change in position of the writing lever.)

The hyperventilation caused a slight fall in blood pressure with the exception of one animal, in which it produced a marked rise. During the infusion of lactic acid, the falls of blood pressure were markedly increased; the rises were abolished.

TABLE 10.—*Stimulation of the Crural Nerve Without and With Want of Oxygen* *

		Gas Mixture Inhaled				Blood Pressure				
Experiment	Period of Experiment	Oxygen, per Cent	Nitrogen, per Cent	Duration, Seconds	Duration of Stimulus, Seconds	During and Before Stimulus	During and After Stimulus	Increase	Average Increase	Comparison of Average Results
46	a		Air		5	40	44	4	4	b = a+3
					5	40	44	4		
	b	6	94	60	5	45	54	9	7	
					5	43	48	5		
47	a		Air		5	108	110	2	2	b = a+8
	b	6	94	35	5	120	130	10	10	
48	a		Air		5	124	170	46	46	b = a+26
					5	116	161	45		
	b	10	90	20	5	130	213	83	72	
					5	152	214	62		

* The single stimuli were done at intervals of sixty seconds.

TABLE 11.—*Stimulation of the Crural Nerve Without and With Infusion of Lactic Acid*

		Lactic Acid Infused			Blood Pressure				
Experiment	Period of Experiment	Concentration, per Cent	Volume, Cc. per Minute	Duration of Stimulus, Seconds	Before Stimulus	During and After Stimulus	Increase	Average Increase	Comparison of Average Results
49	a	.....	..	10	106	113	7	7	b = a+6
				10	107	112	5		
				10	107	116	9		
	b	n/20	1	10	100	115	15	13	
				10	99	110	11		
				10	98	111	13		
50	a	.....	..	5	120	191	71	71	b = a+19
	b	n/20	1	5	116	206	90	90	
51	a	.....	..	5	110	151	41	25	b = a+37
				5	104	122	18		
				5	98	114	16		
	b	n/20	1	5	123	203	80	62	
				5	115	176	61		
				5	116	178	62		
				5	109	165	56		
				5	125	176	51		

Sensitive Stimuli and Want of Oxygen (table 10).—The effect of peripheral sensitive stimuli on blood pressure is increased by a shortage of oxygen in the inhaled gas mixture.

Sensitive Stimuli and Infusion of Lactic Acid (table 11).—The increasing effect of peripheral stimuli on blood pressure is intensified during perfusion of the brain with lactic acid. In experiment 51, the evident parallelism of responses in blood pressure and respiration proves the central nervous character of the vasomotor response.

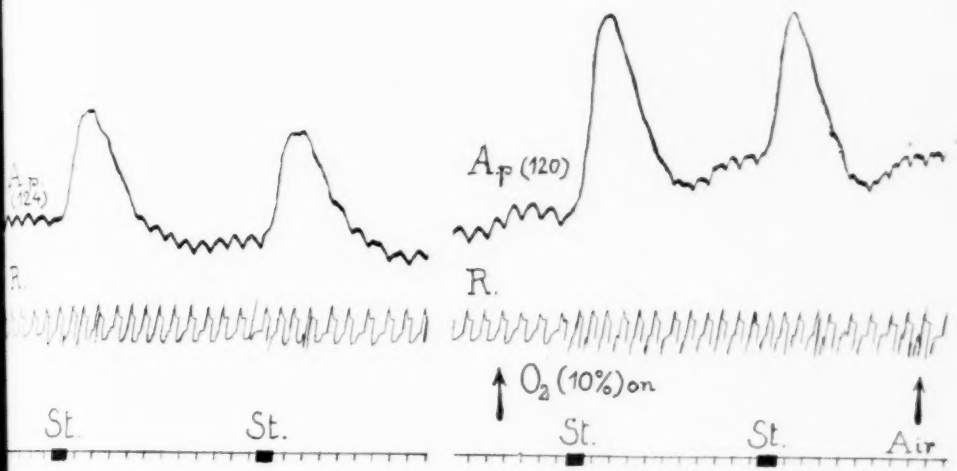

Fig. 10 (experiment 48).—Effect of stimulation of the crural nerve increased by the want of oxygen.

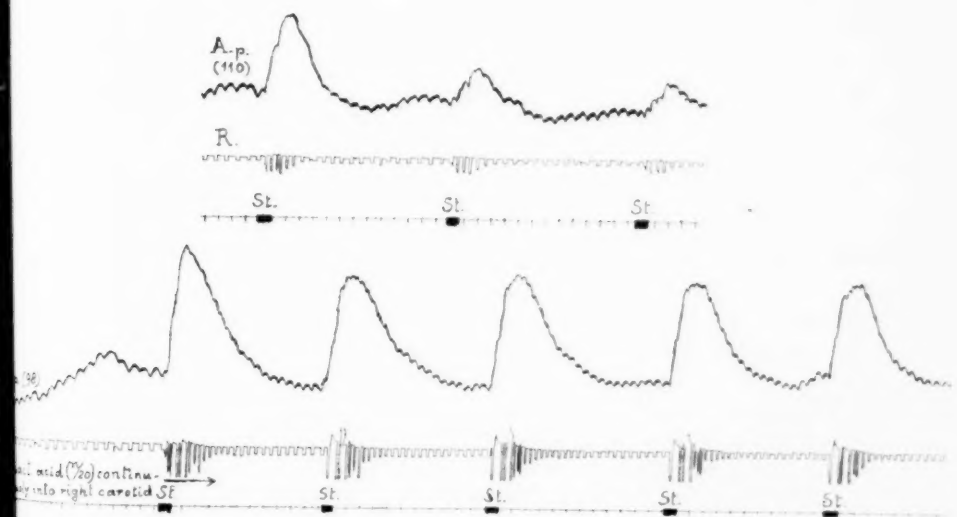

Fig. 11 (experiment 51).—Effect of stimulation of the crural nerve increased by the infusion of lactic acid.

Epinephrine and Want of Oxygen (table 12).—Want of oxygen was produced by complete shutting off of the respiratory air supply, which gives, of course, a combined effect of want of oxygen and accumulation of carbon dioxide, or by the administration of an oxygen-nitrogen mixture with a low oxygen concentration.

TABLE 12.—*Effect of Epinephrine Normally and During Want of Oxygen*

Experiment	Period of Experiment	Epinephrine Injected: Amount, Mg.	Epinephrine Injected: Place	Gas Mixture Inhaled: Oxygen, per Cent	Gas Mixture Inhaled: Nitrogen, per Cent	Blood Pressure: Initial	Blood Pressure: Maximum Attained	Blood Pressure: Deviation	Comparison of Results
52	a	0.012	Right carotid	Air		60	116	+56	
	b	.....	.....	0	0	66	172		b = a—78
		0.012	Right carotid	0	0	172	150	—22	
53	a	0.015	Right carotid	Air		60	94	+34	
	b	.....	.....	0	0	60	144		b = a—62
		0.015	Right carotid	0	0	144	116	—28	
54	a	0.006	Femoral vein	Air		108	164	+56	
	b	.....	.....	10	90	60	150		b = a—72
		0.006	Femoral vein	10	90	150	134	—16	
55	a	0.006	Femoral vein	Air		116	146	+30	
	b	.....	.....	5	95	90	136		b = a—38
		0.006	Femoral vein	5	95	134	126	— 8	
56	a	0.012	Femoral vein	Air		90	144	+54	
	b	.....	.....	5	95	90	128		b = a—28
		0.012	Femoral vein	5	95	128	154	+26	

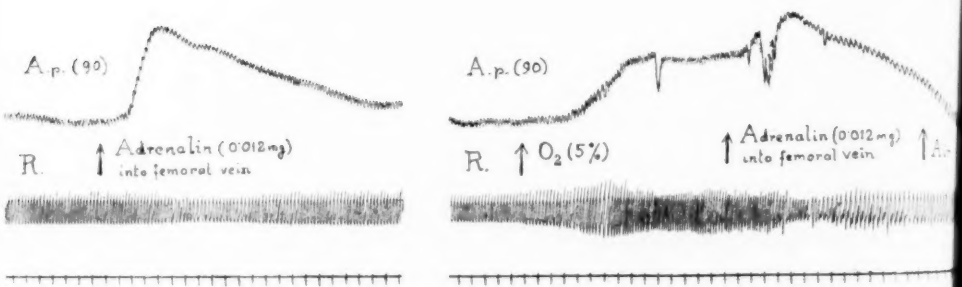

Fig. 12 (experiment 56).—Effect of epinephrine altered by the want of oxygen.

In four of five experiments, the increasing effect of epinephrine on the blood pressure was inverted into a fall during want of oxygen; in one experiment (56), it was diminished by 50 per cent.

Epinephrine and Infusion of Lactic Acid (table 13).—In contrast to the conditions during the shortage of oxygen, the effect of epinephrine on the blood pressure is only insignificantly altered during perfusion of the brain with lactic acid.

TABLE 13.—*Effect of Epinephrine Normally and During Infusion of Lactic Acid*

Experiment	Lactic Acid Infused: Period of Experiment	Concentration, per Cent	Volume, Cc. per Minute	Duration, Min.	Epinephrine Injected: Amount, Mg.	Place	Blood Pressure: Initial	Maximum Attained	Deviation	Comparison of Results
57	a	...	....	..	0.006	Femoral vein	112	132	+20	
	b	7.5	0.07	30	0.006	Femoral vein	148	170	+22	b = a+2
58	a	...	....	..	0.012	Femoral vein	114	164	+50	
	b	7.5	0.07	20	0.012	Femoral vein	140	185	+45	b = a−5
59	a	...	....	..	0.012	Femoral vein	102	160	+58	
	b	5.0	0.15	5	0.012	Femoral vein	138	180	+42	b = a−16
60	a	...	....	..	0.012	Femoral vein	130	182	+52	
	b	7.5	0.15	10	0.012	Femoral vein	164	214	+50	b = a−2

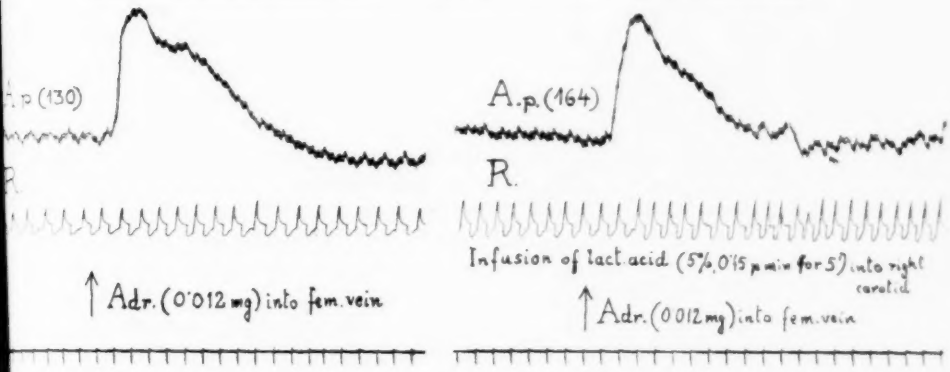

Fig. 13 (experiment 60).—Effect of epinephrine unaltered by the infusion of lactic acid.

COMMENT

The experiments described show a striking accordance of characteristic symptoms in clinical essential hypertension and in the experimental conditions that were intended to imitate the assumed pathogenic causes of essential hypertension, namely, need of oxygen and the presence of an increased amount of lactic acid within the cerebral vasomotor center region. In my experiments there was used a cutting down of the oxygen supply to the whole body. Hence also the peripheral circulatory apparatus was exposed to this abnormal condition at the same time. It has been stated by various authors (Mathison,[20] Romanese,[67] McGinty and Gesell,[26] Gollwitzer-Meier [68] and others) that general anoxemia in consequence of the diminished inhalation of oxygen leads to an increase of the arterial blood pressure. Gollwitzer-Meier,[68] who used for her experiments concentrations of oxygen within about the same range as I (from 14 to 6 per cent), observed a slight increase of the

67. Romanese, R.: Boll. d. Soc. ital. di biol. sper. **2**:887, 1928.
68. Gollwitzer-Meier, K.: Arch. f. d. ges. Physiol. **220**:434, 1928.

time volume of the heart, to which she attributed, however, less importance for this increase of blood pressure than to an irritation of the vasomotor centers, an opinion which has also been expressed by Mathison,[20] A. Loewy [13] and others. Dale and Richards [69] have given evidence for it by tying up both carotids and one vertebral artery; Gurdjian [22] demonstrated it by the effect of the local application of sodium cyanide on the brain stem in the vasomotor region, which prevents oxidation and causes a strong rise of blood pressure. The action of shortage of oxygen on the tonus of the vasomotor centers seems, however, not to be direct but due to the formation and accumulation of acid substances, especially of lactic acid as has been shown similarly for the respiratory center by Haldane and his collaborators,[50] Winterstein [70] and Gesell.[33] Besides, there occurs during general anoxemia, of course, a formation of lactic acid in the other parts of the body (Araki,[71] Ryffel [72] and others) which will reach the brain by the blood stream. With regard to the prevailing central effect of anoxemia on blood pressure, it is justifiable to consider the effect on the blood pressure of breathing low concentrations of oxygen as practically analogous to that of a diminished local oxygen supply to the vasomotor centers.

The injection of acids into the central stump of the right carotid artery, as done by Mathison [20] and Gollwitzer-Meier,[34] is a suitable way to let these substances act on the brain tissue, although they are, of course, also distributed to a certain extent in the peripheral vascular system. The latter fact, however, is not of great practical importance. It is true that acids exert a certain dilating action on the peripheral vessels (Fleisch [73] and others), but at the same time their stimulating influence on the vasoconstrictory centers is so strong that it overcomes the dilatation entirely and leads to a considerable rise of blood pressure (Cobet,[14] Ganter [74]). Thus the results of my experiments with injection into the carotid artery are to be considered as essentially due to perfusion of the brain stem.

A long-lasting shortage of oxygen in the inhaled air is not apt to produce an equally long-lasting rise in blood pressure, because of the weakening of the heart, while it is possible to maintain the blood pressure on an abnormally high level during hours by prolonged infusion of lactic acid (experiments 30 to 35).

---

69. Dale, H. H., and Richards, A. N.: J. Physiol. **63**:101, 1927.

70. Winterstein, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 9, p. 515.

71. Araki: Ztschr. f. physiol. Chem. **15**:335 and 546, 1891; **19**:422, 1894.

72. Ryffel: J. Physiol., vol. 39, Proc. Physiol. Soc., p. xxix, 1909-1910.

73. Fleisch: Arch. f. d. ges. Physiol. **171**:86, 1918.

74. Ganter, G.: Arch. f. exper. Path. u. Pharmakol. **138**:270, 1928.

The purpose of my experiments, however, was not to state the mere stimulating action of the need of oxygen and of lactic acid, which is well enough known, but to investigate the influence of these factors on the irritability of the vasomotor centers. The latter could be shown to be markedly increased as far as the reaction to increased carbon dioxide in the blood (inhalation of carbon dioxide), to decreased carbon dioxide in the blood (hyperventilation) and to peripheral sensitive stimuli (from the crural nerve) is concerned.

The experiments with inhalation of carbon dioxide (experiments 1 to 15, 19 to 23, 36 to 39) showed a considerably stronger rise of blood pressure if combined with a diminished supply of oxygen or with the infusion of lactic acid (the latter both in short and in prolonged periods), or with the injection of lactic acid into the suboccipital cavity. The rise in blood pressure not only consisted in a mere summation of the effect of anoxemia or lactic acid on one side and the effect of carbon dioxide on the other, but it was almost without exception greater than the mathematical sum of both. The figures found, of course, cannot be considered as an absolute quantitative expression of the dynamic processes in the vascular system, but the fact of a mutual increase of efficiency is evident, especially in such experiments in which one or both factors (oxygen need and lactic acid, respectively), alone did not or almost did not raise the blood pressure but still gave a stronger rise with carbon dioxide than carbon dioxide alone (experiments 4, 10, 12 and 37). This is also the case in the experiments with the injection of lactic acid into the cerebrospinal cavity, which itself produced a rise of blood pressure lasting only a short time, with an early return to or even below the normal level, while it caused a markedly increased effect of the inhalation of carbon dioxide within twenty minutes (experiments 20 to 23). Hence the presence of lactic acid in the center region can be sufficient to intensify the effect of the stimulus of carbon dioxide even if it is too weak to produce any direct effect by itself. The increasing influence of lactic acid on the effect of carbon dioxide was missed only in a state of exceedingly strong excitation of the centers by the infusion of lactic acid and on a very high level of blood pressure (experiment 36).

A few experiments have also been made with acetic acid. It acts in the same way as lactic acid as far as the intensification of the effect of carbon dioxide is concerned, although its own effect on the blood pressure in the concentrations used was rather a slightly depressant one (experiments 16 and 18). The effects of alkali (sodium carbonate) were irregular (experiments 24 to 29). Gesell [33] and Gollwitzer-Meier [34] found a decreasing influence of sodium carbonate injected intravenously

on both blood pressure and respiration. This is not regularly the case with injections into the carotid; on the contrary a considerable rise of blood pressure was sometimes noticed (+25 and +51 mm.; experiments 28 and 29). The influence of sodium carbonate on the effects of carbon dioxide was not uniform, and varied within a wide range between strong increases and decreases. A possible explanation for this behavior might be seen in the statement of Jacobs [75] that even alkaline substances can lead to an acid reaction in the interior of the cells which they surround. For instance, bicarbonate buffer mixtures let the bicarbonate radical pass through the cell membrane, and as a matter of fact Gesell [33] found that the intravenous injection of sodium bicarbonate, although itself alkaline, increases the hydrogen ion concentration of the cerebrospinal fluid and acts like an acid on the respiratory center. Gollwitzer-Meier [34] observed the same concerning the effect of bicarbonate on the blood pressure. One can assume, therefore, that a combination of sodium carbonate with buffers of the blood, with the normal amount of carbon dioxide present, and especially with increased amounts of carbon dioxide during the inhalation of carbon dioxide, might form sodium bicarbonate and so lead to the paradoxical acid-like effect in varying degrees which probably mainly depend on the mutual relations in concentration ($Na_2CO_3 + CO_2 + H_2O = 2NaHCO_3$).

Hyperventilation causes a loss of carbon dioxide and usually a more or less marked fall of blood pressure, which has been attributed partly to mechanical changes in the circulation (Vincent and Cameron,[76] Janeway and Ewing,[77] Hill and Flack,[78] Vincent and Thompson,[79] Rappaport [31]) and partly to the diminished stimulus of carbon dioxide on the vasomotor centers (Henderson,[80] Dale and Evans,[81] Hill and Flack,[78] Vincent and Thompson [79]). Dale and Evans,[81] in accordance with Henderson's conception, considered the content of the blood in undissociated carbon dioxide as essentially important for the tone of the vasomotor centers. Stross [82] did not find, however, a moderate loss of carbon dioxide of considerable influence on the blood pressure. In my experiments (40 to 45) which have been done in curarized decerebrate animals with artificial respiration, the artificial increase of respiration amounted only to from 26 to 68 per cent. With the exception

75. Jacobs, M. H.: Am. J. Physiol. **58**:457, 1920-1921.
76. Vincent and Cameron: Quart. J. Exper. Physiol. **9**:64, 1915.
77. Janeway and Ewing: Am. J. Surg. **59**:160, 1914.
78. Hill and Flack: J. Physiol. **40**:354, 1910.
79. Vincent, S., and Thompson, J. H.: J. Physiol. **66**:307, 1928.
80. Henderson, Y.: Am. J. Physiol. **21**:126, 1908.
81. Dale, H. H., and Evans, C. L.: J. Physiol. **56**:125, 1922.
82. Stross, W.: Arch. f. exper. Path. u. Pharmakol. **131**:18, 1928.

of one animal in which each period of hyperventilation produced a considerable rise of blood pressure for unknown reasons, there was a slight drop of blood pressure during increased respiration. During the infuson of lactic acid into the right carotid artery, this hyperventilatory fall was markedly deeper, and the exceptional rises of blood pressure (in the animal mentioned) were checked if hyperventilation was done during the infusion of lactic acid. Hence the latter causes, both absolutely and relatively, a stronger decreasing effect of hyperventilation on the blood pressure than it appears to do under normal conditions.

In summarizing all the experiments discussed, one can conclude that the sensitivity of the vasomotor centers to changes in the carbon dioxide content of the blood (both to increase and to decrease of carbon dioxide) is considerably strengthened by the presence of lactic acid in the region of the vasomotor center and as a consequence of local want of oxygen.

This increased sensitivity, however, is not only evidenced in chemically stimulating tests as carbon dioxide but also in purely nervous stimuli from the periphery. Faradic stimulations of the crural nerve (central stump) caused considerably higher rises in blood pressure when they were combined with inhalation of a low percentage of oxygen or with infusion of lactic acid (experiments 46 to 51).

Experiments that were done for comparing the action of epinephrine on the blood pressure under normal conditions and under the influence of lactic acid and want of oxygen showed that the ordinary rising effect was inverted or at least considerably weakened during the shortage of oxygen, while it was very little altered during artificial hypertension produced through the infusion of lactic acid. To understand this peculiar behavior one has to consider the action of epinephrine on the circulation of the brain. The literature on this topic is fairly contradictory. Some authors claim an almost complete lack of innervation of the vessels of the brain and a passive dilatation of these vessels as a consequence of a rise in the systemic blood pressure through epinephrine (Schneider [83] and others). In recent work Forbes and Wolff [84] showed, however, that this is not entirely true, at least as far as the vessels on the surface of the brain are concerned. These vessels contract under the direct local influence of epinephrine, while they become dilated if their com-

83. Schneider, E. C.: Am. J. Physiol. **84**:202, 1928.

84. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

paratively weak contracting power is overcome by a stronger rise in systemic pressure. Dale and Richards [69] stated that doses of epinephrine that increase the blood pressure under normal conditions produce a fall of pressure if the blood supply to the brain is cut down by tying up the carotids and one vertebral artery and if the vasomotor centers are thus irritated. They attributed this phenomenon to an improvement of the poor circulation in the brain through the action of epinephrine. The results of my experiments can hardly be more easily explained than by the same assumption of an increased flow of blood through the brain —at least through the brain stem—under the influence of epinephrine.

(*a*). The diminution of oxygen in the inspiratory air leads to the accumulation of lactic acid in the centers and increased blood pressure. If epinephrine increases the circulation through the centers, the lactic acid will be removed, and the blood pressure will fall toward the normal.

(*b*). If lactic acid is perfused through the region of the vasomotor center by adding it to the arterial blood, and if the blood pressure is thus increased, an increased perfusion of the brain will, of course, not diminish the lactic acid within the center region; no considerable alteration of the pressure-raising effect of epinephrine will take place.

COMPARISON WITH CLINICAL CONDITIONS

As mentioned, the main purpose of my experiments has been the experimental imitation of characteristic symptoms of clinical hypertension. These characteristic clinical symptoms are as follows: (1) elevated blood pressure, (2) hypersensitivity of the vasomotor centers to changes in the carbon dioxide content of the blood by the inhalation or exhalation of carbon dioxide, (3) hypersensitivity of the centers to peripheral nervous stimuli and (4) reversion or weakening of the effect of epinephrine on the blood pressure.

There was, of course, no possibility of producing an elevation of blood pressure for a period to be compared with the clinical hypertension that is often maintained during years. Still the fact that a considerable increase of blood pressure could be produced for as long as two hours by prolonged infusion of lactic acid proves that a chemical stimulus of this kind does not cause only short-lasting effects with rapidly following fatigue of the stimulated centers. The assumption of a local stimulating chemical factor in the region of the vasomotor center of hypertonic persons, therefore, seems to be justified from the beginning.

The hypersensitivity to the inhalation of carbon dioxide that could be clearly demonstrated in the experiments under the conditions which cause the presence of abnormal amounts of lactic acid in the vasomotor

region seems to be less marked if the center is in a state of exceedingly strong excitation caused by the lactic acid itself and if the blood pressure level is very high. I have observed the same thing in men. As a rule, there is a markedly stronger response of blood pressure to the inhalation of carbon dioxide in hypertonic than in normal persons (the increases in hypertonic persons are on an average three times higher than in normal persons), but in persons with a blood pressure above 200 mm. the absolute increase was not as high as in persons with a pressure between 143 and 179 mm. It seems probable that in spite of an increased irritability the effects of a definite additional stimulus will not transgress a certain upper limit. On the other hand, the artificial hyperirritability was not always connected with a visible state of hyperirritation. In some experiments the lactic acid or reduced oxygen alone did not raise the blood pressure, yet the effect of the added stimulus of carbon dioxide was considerably increased. This state would correspond to the initial period of many "latent" hypertonic cases with a blood pressure that is not definitely increased under normal conditions and during rest, but that responds to all kinds of stimuli easier and with higher rises than in normal cases.

In normal men moderate hyperventilation does not regularly cause a fall in blood pressure, and if it occurs it is much less marked than in hypertonic persons. Collin, Densham and Wells,[4] Schneider[5] and I[1] observed a drop of blood pressure in only 40 per cent of normal cases. On the other hand, in 100 per cent of hypertonic patients examined I[1] have observed an average drop of 28 mm., maximum 60 mm., within from fifteen to thirty minutes. I[1] have given evidence that this effect is due to an especially strong reaction of the vasomotor centers in (not nephritic) hypertension to a loss of carbon dioxide and not to mechanical factors, as Rappaport[3] suggested. The analogous behavior of animals supports this conception. As the mechanical conditions were exactly the same in hyperventilation before and during artificial hypertension caused by lactic acid, there was a greater fall in blood pressure during artificial hypertension. A further analogy with clinical cases is the fact that hypersensitivity to hyperventilation in absence of any visible irritation (without an increased blood pressure level) was seen in one of the experiments and in several cases of latent hypertension in men with a more or less normal initial blood pressure at the time of the examination but with a history of attacks of high blood pressure.

The characteristic hypersensitivity to all kinds of peripheral stimuli that appears so frequently in cases of hypertension (Pal,[38] Curschmann[10] and others) corresponds to the considerable artificial increase of blood pressure response to sensitive stimuli during my experiments.

It is probable also that the increased response of blood pressure to psychic emotions in hypertonic patients might occur on the same basis—reflex transmission of central nervous excitements to the hypersensitive vasomotor centers.

The peculiarities of the effect of epinephrine on hypertonic persons and its frequent weakness or paradoxic inversion can possibly be explained as due to a removal of accumulated lactic acid from the vasomotor center through the improvement of the blood flow through this region under the influence of epinephrine. This explanation would not be incompatible with Kylin's [61] conception of a general change in the tonus of the vasomotor nervous system as the basis of the paradoxic effect of epinephrine on hypertonic persons.

My experimental results show that the vasomotor center reacts in about the same way that Haldane,[50] Winterstein,[70] Gesell,[33] Straub [36] and others have shown that the respiratory center does. The clinical syndrome of "cerebral dyspnea" has been described by Straub [36] and von Romberg.[37] It has been conceived as due to local disturbances of the circulation of the respiratory center. Von Romberg emphasized the frequency of this feature in cases of hypertension, which appears natural if one assumes the same pathogenic factors to be responsible also for the development of hypertension, as is suggested by my experiments. It is rather surprising that the parallelism of hypertension and "cerebral dyspnea" is not more regular. A satisfactory explanation for this discrepancy, which as a matter of fact is almost more frequently observed than the simultaneous occurrence of both features, cannot be given at present. There are, however, possible explanations, as, for instance, a (although improbable) local separation of the vasomotor centers and the respiratory centers which would be considerable enough to allow the development of vascular troubles in only one of them, the other remaining unaffected, or a generally lower irritability of the respiratory center, which is suggested by some of my experiments in which the effects on blood pressure appear markedly stronger than those on respiration.

A summary of the conception of the origin of hypertension as it is suggested by my experiments could be formulated as follows: A primary disturbance of the blood flow through the region of the vasomotor center (or temporarily by vessel spasms or continuously by sclerotic alterations of the vessels of this region) leads to a diminished supply of oxygen and the subsequent formation and accumulation of abnormal amounts of lactic acid within the nerve cells of the centers. In the first stages the presence of lactic acid produces only an increased irritability of the centers—the pressure is not yet constantly high, but rises abnormally easily and strongly. Little by little the alteration of the center vessels and consequently the accumulation of lactic acid

develop enough to produce a constant irritation of the centers. The pressure level rises. At the same time the hyperirritability persists, and all kinds of stimuli—sensitive sensations, psychic emotions, muscular activity and even the normal carbon dioxide content of the blood—contribute to the increase of blood pressure and its lability. If a certain upper limit is attained, the hyperirritability can become less marked again because of the prevailing effect of the strong irritation through lactic acid in comparison to which the other stimuli lose in efficiency—"fixed hypertension." Factors that temporarily improve the blood flow through the centers might cause a fall in blood pressure (for instance, epinephrine or, as I have found in the majority of hypertonic persons, diathermy of the brain stem).

The question of the causal connection between hypertension and general arteriosclerosis cannot be discussed here. It may be mentioned that in some cases there could be a primary localized sclerosis within the brain stem (isolated arteriosclerosis of the brain is not a rare occurrence) with subsequent hypertension that would lead to a more generalized arteriosclerosis, kidney conditions, etc., and as a vicious circle to further deterioration in the region of the vasomotor centers. The essential primary factors of the whole process, however, are unknown. Kylin's [61] investigations concerning the ion balance and its influence on the vegetative nervous system seem to show a promising way of discovering the origin of pathologic conditions of the vessels of the nerves. On the other hand, the anatomic observations of Bordley and Baker [17] and others concerning sclerosis of the vessels of the vasomotor centers in hypertension and the large amounts of lactic acid found in brain tissue after shortage of oxygen by McGinty and Gesell,[26] Haldi, Ward and Woo [28] and Cobet [27] can be considered as a basis for the validity of the conception mentioned.

SUMMARY

In decerebrate cats with the vagi cut, the following experimental results were obtained:

1. There was a strong increase of the arterial blood pressure for a period up to two hours by the continuous perfusion of the brain stem with blood containing abnormally high amounts of lactic acid.

2. Hyperirritability of the vasomotor centers resulted under the influence of a shortage of oxygen or perfusion with lactic acid, or with the injection of lactic acid into the suboccipital cavity. The inhalation of carbon dioxide causes a considerably greater rise and the hyperventilation (loss of carbon dioxide) a greater fall in blood pressure under these conditions than occur under normal conditions.

3. Sensitive stimuli cause higher rises of blood pressure during the conditions mentioned than they do normally.

4. The effect of epinephrine is considerably weakened and inverted during the lack of oxygen; it is scarcely altered during perfusion with lactic acid.

5. Acetic acid increases the irritability of the vasomotor center in the same way as lactic acid; alkali (sodium carbonate) gives irregular effects.

6. These experimental results correspond to the following characteristic features of essential hypertension: (1) high blood pressure; (2) hypersensitivity to the inhalation of carbon dioxide (abnormal increase of blood pressure) and to hyperventilation (abnormal fall of blood pressure); (3) hypersensitivity to peripheral sensitive stimuli and (4) weakened or inverted effect of epinephrine.

7. The conclusion was reached that the symptoms of "essential" (not nephritic) hypertension can be considered due to the local need of oxygen and the accumulation of lactic acid within the vasomotor centers of the brain stem as a consequence of local circulatory disturbances (spasms, sclerosis). The actual level of the blood pressure in hypertension would accordingly be composed of the sum of the stimulus through lactic acid plus the pathologically increased responses to the stimulus of the normal carbon dioxide tension of the blood and of different kinds of sensitive and emotional stimuli.

SERUM AND PLASMA BILIRUBIN

A COMPARATIVE QUANTITATIVE STUDY OF ONE HUNDRED CASES *

MENDEL JACOBI, M.D.

REUBEN FINKELSTEIN, M.D.

AND

RUDOLPH KURLEN

BROOKLYN

The van den Bergh reaction [1] for bile pigment in the blood was introduced in 1918. As originally proposed, the determinations were made with the blood serum. During the twelve years that have elapsed, the test has received general and widespread acceptance. Today, both in the original technic and in the modifications, most important of which is the Thannhauser and Andersen method,[2] serum is still employed.

McNee and Keefer [3] were the first to suggest the use of plasma instead of serum. These workers applied the original van den Bergh technic to the plasma obtained from oxalated blood in the proportion of 0.2 cc. of 10 per cent potassium oxalate to from 10 to 15 cc. of whole blood. The results led them to assert that plasma and serum may be utilized equally well.

Shay and Schloss [4] disagreed with these observers. In a series of eleven simultaneous examinations of serum and plasma by the original van den Berg and the Thannhauser and Andersen methods, they found an agreement of the readings for the serum and plasma in only four instances. In fourteen instances, the reading for the serum were greater by amounts ranging from 0.1 to 7.5 units; in three instances, the readings for the plasma were of greater magnitude, of the order of 0.1 to 0.4 unit.

In view of these diametrically opposed opinions, and because the original suggestion was not accompanied by tables to illustrate the

* Submitted for publication, Sept. 15, 1930.

* From the Pathological Laboratories of the Brownsville and East New York Hospital, Brooklyn.

1. van den Bergh, H.: Der Gallenfarbstoffe im Blute, Leiden, S. C. van Doesburgh, 1918.

2. Thannhauser, S. J., and Andersen, E.: Methodik der quantitativen Bilirubinbestimmung in menschlichen Serums, Deutsches Arch. f. klin. Med. **137**: 179 (Aug.) 1921.

3. McNee, J. W., and Keefer, C. S.: Clinical Value of van den Bergh Reaction for Bilirubin in Blood, with Notes on Improvements in Its Technique, Brit. M. J. **2**:52 (July 11) 1925.

4. Shay, H., and Schloss, E. M.: van den Bergh Reaction: Comparison of Technics, J. Lab. & Clin. Med. **15**:292, 1929.

figures on which the opinion was based while the dissenting opinion was based on so few determinations, we decided to reinvestigate the subject. If plasma could be substituted for serum, it would mean a considerable saving of time for the laboratory; the performance of the reaction would be facilitated as it could then be carried out with oxalated blood taken in the course of routine chemical examinations, and additional inconvenience to the patients incident to an added venipuncture would be avoided. To this end, we performed simultaneous determinations quantitatively on 100 consecutive and unselected serums and plasmas from cases in the hospital and from the dispensary. The Thannhauser and Andersen modification was used in all instances, since with that

TABLE 1.—*Differences Between Simultaneous Readings for the Serum and the Plasma Calculated from Table 3 of Shay and Schloss*

	van den Bergh Technic	Thannhauser and Andersen Technic
Readings agreeing	4	0
Readings disagreeing	7	11
Serum readings greater (units)	6	8
0.1	1	0
0.2	0	1
0.4	0	1
1.2	1	0
1.3	2	0
1.4	0	1
1.7	0	1
3.0	0	1
4.1	1	0
4.2	1	0
4.3	1	0
5.4	0	1
7.4	0	1
7.5	0	1
Plasma readings greater (units)	1	2
0.1	1	0
0.2	0	1
0.4	0	1

method all the azobilirubin could be retained for estimation in the supernatant fluid, and because the discrepancies noted by Shay and Schloss were both more frequent and of greater magnitude. Muller's cobalt sulphate standard [5] was used throughout.

Table 2 shows a remarkable agreement of the readings for both the serum and the plasma. In each of the first fifty determinations, coupling was allowed to take place for one-half hour before the proteins were precipitated. In the latter half of the series (specimens 50 to 75) coupling of the diazo reagent and serum was allowed for sixty minutes, and of reagent and plasma for thirty minutes; while in specimens 76 to 100, coupling of the plasma and reagent was allowed for sixty minutes and of the serum and the reagent for thirty minutes. In neither of these groups could we detect any differences in readings not

5. Quoted from Hawk and Bergeim: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, 1926; footnote, p. 396.

found in the group with coupling of equal duration. In fact, the largest difference in readings observed in the entire series, 0.8 unit, occurred in the group with equitemporal coupling (specimen 20).

An analysis of our figures (table 3) shows exact agreement in 70 per cent of our specimens. In the 30 per cent in which the readings did not agree, an approximately equal number of specimens showed

TABLE 2.—*Simultaneous Determinations of the Bilirubin of One Hundred Unselected and Consecutive Serums and Plasmas*

Specimen Number	Plasma Reading, Units	Serum Reading, Units	Specimen Number	Plasma Reading, Units	Serum Reading, Units
1	0.3	0.3	51	0.2	0.2
2	0.2	0.2	52	No reaction	No reaction
3	0.6	0.6	53	1.2	1.2
4	0.4	0.4	54	3.1	3.2
5	0.5	0.4	55	0.2	0.2
6	No reaction	No reaction	56	1.1	1.0
7	6.2	6.2	57	0.3	0.3
8	4.9	5.0	58	0.2	0.2
9	1.3	1.2	59	1.8	2.0
10	1.0	1.1	60	0.5	0.5
11	1.0	1.0	61	1.5	1.5
12	0.3	0.3	62	0.1	0.2
13	0.4	0.3	63	0.2	0.2
14	5.5	5.6	64	0.2	0.2
15	7.5	7.5	65	0.1	0.1
16	8.3	8.2	66	0.1	0.1
17	10.0	10.4	67	5.3	5.2
18	2.4	2.4	68	12.0	11.8
19	0.6	0.6	69	0.5	0.5
20	16.0	16.8	70	0.2	0.2
21	7.0	6.8	71	2.0	2.1
22	0.3	0.3	72	0.2	0.2
23	0.3	0.2	73	0.6	0.6
24	0.3	0.2	74	0.8	0.8
25	0.2	0.2	75	0.9	0.8
26	0.5	0.5	76	2.8	2.9
27	No reaction	No reaction	77	0.3	0.3
28	No reaction	No reaction	78	1.4	1.3
29	0.6	0.6	79	0.2	0.2
30	0.4	0.5	80	0.1	0.1
31	0.2	0.2	81	0.3	0.3
32	0.1	0.1	82	0.4	0.3
33	0.2	0.2	83	0.3	0.3
34	1.1	1.1	84	0.5	0.5
35	No reaction	No reaction	85	0.4	0.4
36	1.4	1.5	86	0.2	0.2
37	6.2	6.2	87	0.6	0.6
38	No reaction	No reaction	88	6.2	6.2
39	1.1	1.1	89	0.4	0.3
40	2.7	2.5	90	5.0	5.1
41	1.0	1.0	91	0.3	0.4
42	10.0	10.0	92	0.2	0.2
43	No reaction	No reaction	93	0.5	0.5
44	2.5	2.4	94	0.3	0.3
45	0.2	0.3	95	4.1	4.1
46	0.2	0.2	96	9.5	9.5
47	0.1	0.1	97	16.0	16.0
48	0.8	1.0	98	0.3	0.3
49	0.4	0.4	99	6.2	6.2
50	0.5	0.5	100	0.1	0.1

higher readings for the serum (in 16 per cent) and higher readings for the plasma (in 14 per cent), a division further borne out when the readings were grouped according to their magnitude. Thus in the group of readings between 0.6 and 1 unit, 66 per cent agreed exactly (eight of twelve readings); of the remaining 33 per cent (four of twelve), the reading for the serum was greater than that for the plasma

figures on which the opinion was based while the dissenting opinion was based on so few determinations, we decided to reinvestigate the subject. If plasma could be substituted for serum, it would mean a considerable saving of time for the laboratory; the performance of the reaction would be facilitated as it could then be carried out with oxalated blood taken in the course of routine chemical examinations, and additional inconvenience to the patients incident to an added venipuncture would be avoided. To this end, we performed simultaneous determinations quantitatively on 100 consecutive and unselected serums and plasmas from cases in the hospital and from the dispensary. The Thannhauser and Andersen modification was used in all instances, since with that

TABLE 1.—*Differences Between Simultaneous Readings for the Serum and the Plasma Calculated from Table 3 of Shay and Schloss*

	van den Bergh Technic	Thannhauser and Andersen Technic
Readings agreeing	4	0
Readings disagreeing	7	11
Serum readings greater (units)	6	8
0.1	1	0
0.2	0	1
0.4	0	1
1.2	1	0
1.3	2	0
1.4	0	1
1.7	0	1
3.0	0	1
4.1	1	0
4.2	1	0
4.3	1	0
5.4	0	1
7.4	0	1
7.5	0	1
Plasma readings greater (units)	1	2
0.1	1	0
0.2	0	1
0.4	0	1

method all the azobilirubin could be retained for estimation in the supernatant fluid, and because the discrepancies noted by Shay and Schloss were both more frequent and of greater magnitude. Muller's cobalt sulphate standard [5] was used throughout.

Table 2 shows a remarkable agreement of the readings for both the serum and the plasma. In each of the first fifty determinations, coupling was allowed to take place for one-half hour before the proteins were precipitated. In the latter half of the series (specimens 50 to 75) coupling of the diazo reagent and serum was allowed for sixty minutes, and of reagent and plasma for thirty minutes; while in specimens 76 to 100, coupling of the plasma and reagent was allowed for sixty minutes and of the serum and the reagent for thirty minutes. In neither of these groups could we detect any differences in readings not

5. Quoted from Hawk and Bergeim: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, 1926; footnote, p. 396.

found in the group with coupling of equal duration. In fact, the largest difference in readings observed in the entire series, 0.8 unit, occurred in the group with equitemporal coupling (specimen 20).

An analysis of our figures (table 3) shows exact agreement in 70 per cent of our specimens. In the 30 per cent in which the readings did not agree, an approximately equal number of specimens showed

TABLE 2.—*Simultaneous Determinations of the Bilirubin of One Hundred Unselected and Consecutive Serums and Plasmas*

Specimen Number	Plasma Reading, Units	Serum Reading, Units	Specimen Number	Plasma Reading, Units	Serum Reading, Units
1	0.3	0.3	51	0.2	0.2
2	0.2	0.2	52	No reaction	No reaction
3	0.6	0.6	53	1.2	1.2
4	0.4	0.4	54	3.1	3.2
5	0.5	0.4	55	0.2	0.2
6	No reaction	No reaction	56	1.1	1.0
7	6.2	6.2	57	0.3	0.3
8	4.9	5.0	58	0.2	0.2
9	1.3	1.2	59	1.8	2.0
10	1.0	1.1	60	0.5	0.5
11	1.0	1.0	61	1.5	1.5
12	0.3	0.3	62	0.1	0.2
13	0.4	0.3	63	0.2	0.2
14	5.5	5.6	64	0.2	0.2
15	7.5	7.5	65	0.1	0.1
16	8.3	8.2	66	0.1	0.1
17	10.0	10.4	67	5.3	5.2
18	2.4	2.4	68	12.0	11.8
19	0.6	0.6	69	0.5	0.5
20	16.0	16.8	70	0.2	0.2
21	7.0	6.8	71	2.0	2.1
22	0.3	0.3	72	0.2	0.2
23	0.3	0.2	73	0.6	0.6
24	0.3	0.2	74	0.8	0.8
25	0.2	0.2	75	0.9	0.8
26	0.5	0.5	76	2.8	2.9
27	No reaction	No reaction	77	0.3	0.3
28	No reaction	No reaction	78	1.4	1.3
29	0.6	0.6	79	0.2	0.2
30	0.4	0.5	80	0.1	0.1
31	0.2	0.2	81	0.3	0.3
32	0.1	0.1	82	0.4	0.3
33	0.2	0.2	83	0.3	0.3
34	1.1	1.1	84	0.5	0.5
35	No reaction	No reaction	85	0.4	0.4
36	1.4	1.5	86	0.2	0.2
37	6.2	6.2	87	0.6	0.6
38	No reaction	No reaction	88	6.2	6.2
39	1.1	1.1	89	0.4	0.3
40	2.7	2.5	90	5.0	5.1
41	1.0	1.0	91	0.3	0.4
42	10.0	10.0	92	0.2	0.2
43	No reaction	No reaction	93	0.5	0.5
44	2.5	2.4	94	0.3	0.3
45	0.2	0.3	95	4.1	4.1
46	0.2	0.2	96	9.5	9.5
47	0.1	0.1	97	16.0	16.0
48	0.8	1.0	98	0.3	0.3
49	0.4	0.4	99	6.2	6.2
50	0.5	0.5	100	0.1	0.1

higher readings for the serum (in 16 per cent) and higher readings for the plasma (in 14 per cent), a division further borne out when the readings were grouped according to their magnitude. Thus in the group of readings between 0.6 and 1 unit, 66 per cent agreed exactly (eight of twelve readings); of the remaining 33 per cent (four of twelve), the reading for the serum was greater than that for the plasma

in two instances, and in two others the reading for the plasma exceeded that of the serum. In the group of from 5.1 to 10 units, the exact agreement was 55 per cent (seven of thirteen); equal numbers of those not agreeing were found to show greater readings for the serum than for the plasma and vice versa (three in each instance). In the other two groups, of from 1.1 to 5 and over 10 units, exact agreement

TABLE 3.—*Agreement and Disagreement of the Readings for the Serum and the Plasma; One Hundred Cases*

Magnitude of Reading	All Readings	0.6 to 1 Units	1.1 to 5 Units	5.1 to 10 Units	Over 10 Units
Complete agreement (number)	70	8	5	7	1
Disagreement (number)	30	4	11	6	2
Serum readings greater (in units)	16	2	6	3	1
0.1	12	1	5	2	0
0.2	2	1	1	0	0
0.4	1	0	0	1	0
0.8	1	0	0	0	1
Average differences	0.175				
Plasma readings greater (in units)	14	2	5	3	1
0.1	11	2	4	2	1
0.2	3	0	1	1	0
Average differences	0.121				

TABLE 4.—*Simultaneous Determinations of the Bilirubin in Quadruplicate; Five Cases*

Specimen Number	Plasma Reading, Units	Serum Reading, Units	Difference
37	6.4	6.3	0.1
	6.4	6.2	0.1
	6.2	6.2	0.0
	6.3	6.2	0.1
8	4.9	4.7	0.2
	4.7	4.4	0.3
	4.8	5.1	0.3
	4.6	4.8	0.2
78	1.4	1.6	0.2
	1.6	1.6	0.0
	1.5	1.6	0.1
	1.7	1.8	0.1
71	2.1	2.2	0.1
	2.0	2.3	0.3
	2.4	2.1	0.3
48	2.4	2.4	0.0
	0.8	0.6	0.2
	0.9	0.9	0.0
	1.1	0.8	0.3
	1.0	1.0	0.0
Average differences			0.141

occurred in but 31 and 33 per cent, respectively; the total numbers of specimens are, however, too small to draw any definite conclusions from these numbers. In each of these groups, further, a similar number showed a greater reading for the serum and a greater reading for the plasma (five and one, respectively). It is especially significant to us that, with but one exception (specimen 20), all readings differed by

no more than 0.4 unit. The largest number of differences occurred in the readings differing by 0.1 unit in each of the quantitatively separated subgroups.

To determine the probable error of our experiments, quadruplicate determinations were performed for five serums and plasmas taken at random from the specimens submitted (table 4). These determinations, when made with instruments (colorimeter, standards, chemicals and glassware), coupling conditions and conditions of lighting identical with those used in the entire series, and performed by one of us (R. K.), who performed the actual tests, showed differences ranging from 0 to 0.3 unit. In the entire series the differences were of the same order, from 0.1 to 0.4 unit, with but a single determination (specimen 20) showing a difference of 0.8 unit, a difference so much larger than the others observed as to warrant its omission from the series. Even with this large difference included, the average differences in the greater readings for the serum was 0.175 as compared with 0.121 in the greater readings for the plasma and 0.141 in the quadruplicate determinations. If this excessively large difference is omitted, these figures become 0.133, 0.121 and 0.141, respectively. The average differences between the greater readings for the serum and greater readings for the plasma then become of the order of magnitude as that in the groups for the quadruplicate determination; and the individual differences between the simultaneous readings for the bilirubin in the serum and in the plasma lose their apparent significance.

SUMMARY

1. The results of simultaneous quantitative determinations of bilirubin by the Thannhauser and Andersen modification of the van den Bergh technic in 100 consecutive and unselected cases are reported, and the results are analyzed as to the degree of agreement or disagreement.

2. The readings are shown to correspond in a very high degree, and they indicate that plasma instead of serum may be used with equal accuracy in determinations of bilirubin.

3. The results confirm the statements of McNee and Keefer. They are directly opposed to the figures reported by Shay and Schloss from eleven observations with wide discrepancies in the readings.

4. An increase in the length of time allowed for coupling up to one hour apparently plays no part in the slight quantitative differences noted.

THE FECES OF PATIENTS WITH CHRONIC ARTHRITIS *

ROBERT T. MONROE, M.D.
AND
FRANCIS C. HALL, M.D.
BOSTON

That the gastro-intestinal tract of patients with chronic arthritis is abnormal in some way has long been assumed. Dietary regimens of all sorts have been proposed to correct faulty nutrition. Recent work of a clinical and experimental nature by A. A. Fletcher in Canada, R. McCarrison in England and R. Pemberton in the United States shows rather definitely that these people do best when their intake of vitamins is increased and their intake of carbohydrate reduced. Frequently the colon has been accused of acting as a focus of infection, to eradicate which it has been cleansed by vigorous catharsis or irrigation or by changing its bacterial flora, or it has been removed surgically.

If the intestinal tract is pathologic in any important degree, functionally or anatomically, it would seem that the feces, which are the result of the processes of digestion, absorption and motility, should contain some evidence of that fact. Strangely enough, no such data have been presented in the literature that we have examined. Acid stools are mentioned by some writers as being present in arthritis. Abnormal intestinal rates and "foul, evil-smelling feces" are also mentioned by others,[1] but no statistics of routine examinations on a series of patients are given. Therefore, the present study was undertaken to determine whether ordinary clinical laboratory tests reveal any abnormality in the stools of arthritic patients, and, if so, whether the abnormality be of one or of various types.

Our series consisted of forty patients at the Peter Bent Brigham Hospital, three of whom were seen in the medical wards and the rest in the arthritic clinic in the outdoor department, between October, 1929, and June, 1930. In each case the diagnosis was established by history and physical examination, routine analysis of the blood and urine and roentgenograms of the joints involved. Fifteen cases were considered to represent the so-called atrophic type of chronic arthritis; seventeen, the hypertrophic, and eight, a mixture of the two. Treatment was car-

* Submitted for publication, Sept. 26, 1930.

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

1. Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1930.

ried out under the direction of one of us (F. C. H.). It is beyond the scope of this paper to give the details of it, but the diet that was advised was always one rich in vitamins and rather low in available carbohydrates, totalling approximately 2,500 calories daily.

At each visit each patient was asked to bring in a glass jar the last stool specimen passed, and the tests were all done by one man (R. T. M.). Some patients were more faithful than others in complying with this request, and some were seen oftener than others, so that the number of stools from each person varied considerably. Twelve patients had only 1 stool examined, but 142 specimens were analyzed in all. The intervals between collection also varied considerably, depending on the need for seeing the individual patient. Some cases were followed for only a short time, and others throughout the entire period of nine months. Therefore, since much time is required in the treatment of this disease, no definite conclusions could be arrived at as to the effect of therapy on the character of the feces.

The results are best presented according to the steps in a routine analysis of the stool—consistency, color, reaction, tests for blood and microscopic examination for parasites, starch, muscle fibers and fat.

RESULTS OF EXAMINATION OF STOOLS

Consistency.—The majority of the stools (86 of 142) were mushy and formless. A few (5) were liquid, and the rest (51) were normally soft formed; fourteen of the latter, however, showed mushy areas. Cathartics were a factor in only a few, since their use was denied in all but one case. None was of the type seen in constipation.

Color.—The color was not unusual, except that the mushy stools tended to be rather lighter than the rest. Diet and medication (spinach, carrots, iron) had a great influence on the stools in certain cases.

Reaction.—The reaction was tested by taking up a portion of the specimen on a throat stick and laying on it pieces of fresh red and blue litmus paper which had been moistened in tap water. No attempt was made to determine the hydrogen ion concentration, as it appeared to offer no advantage over this simple and clinically sufficient method. The normal stool so tested is usually neutral or alkaline. In thirty-five (87.5 per cent) of these arthritic cases, there were one or more acid stools. Of the total number of examinations, 91 (64 per cent) were acid, 35 (25 per cent) were neutral and 16 (11 per cent) were alkaline.

Gas.—In eighteen patients, all of whom had acid stools, the formation of gas could be observed grossly. Bubbles were visible on the sides of the glass container, and when the mass was stirred with a throat stick, a crackling noise was made. Generation was so active in several

instances as to blow off the cover when the catch was released. Nine of these patients complained of rumbling and gurgling noises in the abdomen or of an excess of flatus.

Miscellaneous.—Benzidine and gum guaiac tests of occult blood were negative in all except one case, that of a woman in whom the duodenal ulcer had bled recently. Mucus was found in only a few specimens, and small in amount and apparently fresh. No parasites were discovered. Muscle fibers were well digested (rounded ends, absent striations) in all except two stools, which were liquid, probably the result of catharsis. No stool showed an excess of fat macroscopically or microscopically when stained with sudan III.

TABLE 1.—*The Amount of Starch in the Stools of One Hundred and Forty-Two Specimens from Forty Patients with Chronic Arthritis as Compared with Ninety-Seven Specimens from Seventy-One Patients with Other Diseases*

Amount of Starch	Arthritic Group	Miscellaneous Group
None	0	22
Trace	5	31
+	25	18
++	39	19
+++	46	5
++++	27	2
Totals	142	97

Starch.—The presence of an excess of starch was the most outstanding observation in these stools and deserves detailed comment. The method of examining the feces microscopically was as follows: a representative bit was rubbed up in a mortar with tap water to form a rather thin paste. The amount of water used varied, of course, with the consistency of the specimen. One drop of this paste was then placed on each of three glass slides; one was left unstained for a study of muscle fibers, parasites and soaps; sudan III was added to the second and a drop of compound tincture of iodine solution to the third. Cover slips were then applied to secure a thin film and allow the higher powers of the microscope to be used. Starch appears deep blue or black after the addition of iodine; erythrodextrin is red, and cellulose remains gray or black. Most of the starch in these cases was enclosed in vegetable cells, which have easily recognized contours, as shown in many works on clinical pathology. The rest of the starch was seen in the form of small, irregularly shaped masses, sometimes outlined by a trace of cellulose or else apparently free in the suspension. The liberation of this starch may have been due to breakage in the mortar.

It was found to be difficult to estimate the amount of starch with any degree of accuracy. Freshly passed stools from normal persons

on an unselected diet usually show no iodine-staining lumps or only a few in the whole cover slip area when a fecal suspension of uniform density is made, as previously described. The latter was said to represent a trace. A larger amount (+) was roughly held to be 1 particle to every 5 or 6 high power fields; ++ was taken to be 1 in every high power field; +++, 2 to 5 in each field, and ++++, many lumps. On such a quantitative scale, none of the 142 stools from these 40 patients with chronic arthritis showed starch; 5 showed a trace; 25, +; 39, ++; 46, +++, and 27, ++++. If any amount under ++ is said to be not abnormal, 112 stools (79 per cent) still showed an excess of starch, which tended definitely to decrease in all cases in which there was improvement under treatment.

Iodine-Staining Organisms.—These organisms appear as large cocci, round or oval, often in chains of four or six, and stain a deep blue or

TABLE 2.—*The Relative Occurrence of Iodine-Staining Organisms and Positive Fermentation Tests in the Stools of Forty Patients with Arthritis and Seventy-One with Miscellaneous Diseases*

	Arthritic Group				Miscellaneous Group			
	No. of Cases	Per Cent	Stools	Per Cent	No. of Cases	Per Cent	Stools	Per Cent
Iodine-staining organisms	36	90	93	65	16	22	17	17.5
Fermentation test positive	33	82.5	87	60	17	24	19	20

black with iodine. Their nature has not yet been determined. Years ago Schmidt [2] called them *Clostridia*, but he did not identify them further. Kendall [3] associated them with the gas bacillus. Little attention has been paid to them, yet they seem to be intimately concerned with the presence of starch and gas in the stools.

Iodine-staining organisms were seen in the stools of 90 per cent of the arthritic patients in this series; only one examination was made in two of the other four cases and only two examinations in the other two. Ninety-three (65 per cent) of the 142 stools gave positive reactions. The number of these organisms did not vary in proportion to the amount of starch present. Sometimes they were found in enormous numbers in specimens with only a trace or a one plus amount of starch, and once they were absent when the starch was rated as four plus. Their presence proved to be a more reliable indication of a fermenting condition than an excess of starch. No specimen which contained starch

2. Schmidt, A., and Strasburger, J.: Die Faeces des Menschen, Berlin, August Hirschwald, 1903.

3. Kendall, A. I.: Intestinal Intolerance for Carbohydrates, J. A. M. A. **86**: 737 (March 13) 1926.

but not *Clostridia* produced gas; on the other hand, the production of gas was often most active with a little starch and many *Clostridia*. Usually, they were not found after the fermentation test, even though starch remained, and the reaction was still acid. After treatment, they tended to disappear much more slowly than the excess of starch.

Fermentation.—Various methods have been devised for measuring the carbohydrate content of the feces, of which the simplest clinical test is that of Schmidt,[2] who used it to advantage in the diagnosis of fermentative diarrhea. This test was used in our work with certain modifications. The patients were not placed on the Schmidt test diet; instead, stools were accepted that were the result of an unselected diet, often rich in carbohydrates, or of a diet low in starch, after treatment was begun. The apparatus is similar to the Einhorn saccharometer, which is used for the detection of dextrose in the urine, except that it is larger and may be made of an ordinary glass jar and test tube connected by glass tubing. No attempt was made to measure the total amount of gas (carbon dioxide) found; if gas completely displaced the water in the collecting tube at the end of twenty-four hours' incubation and the reaction of the feces remained acid, the test was called positive. Therefore, while the following results may be considered as clinically informative, they cannot be judged according to Schmidt's rules. At first, all specimens were given this test. Later, as those which contained no starch or *Clostridia* were always found to be negative, they were not tested. Some specimens which gave neutral or even alkaline reactions, but which contained starch and *Clostridia*, gave positive reactions and became acid after incubation. One or more fermenting stools were found in thirty-three cases in this series (82.5 per cent). Since in the seven negative cases only ten stools were furnished, it was felt that a greater number of examinations might have increased this percentage. In all eighty-seven stools (60 per cent) gave positive reactions. The results did not correspond to those obtained for patients with any type of arthritis, the atrophic and hypertrophic forms being equally represented on both sides. There was a definite tendency for the test to become negative at a varying interval after treatment was begun. Even on direct questioning, few of the patients complained of symptoms suggesting a fermenting condition.

The question naturally arose whether the same disorder occurred with equal frequency among patients suffering from other chronic diseases. From his experience in the gastro-intestinal clinic in this hospital, the impression obtained by one of us (R. T. M.) was that it was to be found only in patients with true fermentative diarrhea, in certain cases of migraine and rarely in a normal subject who has taken a great excess of starch. To obtain a more definite answer to this

question, however, stools were collected from seventy-one patients in the medical wards, and examined as before. No selection of cases was made. Many types of disease were represented; 10 patients had some form of heart disease; 14, chronic nephritis; 11, peptic ulcer; 11, an acute infection (pneumonia, tonsilitis); 5, pulmonary tuberculosis; 4, cancer; 2, pernicious anemia, and 15, miscellaneous conditions (hyperthyroidism, myxedema, abscess of the lung, etc.). Diet was restricted in only a few cases. It was usually an ordinary "balanced" ration, often containing an increased amount of carbohydrates to force nourishment.

Of the ninety-seven stools examined, one-third were acid (35), one-third neutral (31) and one-third alkaline (31). Twenty-two showed no starch; 31, a trace; 18, +; 19, ++; 5, +++, and 2, ++++. Only 26.8 per cent showed a reaction of ++ or more, as compared to 79 per cent for the arthritic group. Iodine-staining organisms were found in 17 stools (17.5 per cent) in 16 cases (22.5 per cent), roughly one-fourth the frequency in the other group. Fermentation tests gave positive reactions in 19 stools (20 per cent) from 17 patients (24 per cent). This test became negative in all 6 cases in which more than a single stool was examined, and *Clostridia* also disappeared more quickly than from the stools in the first group.

Certain definite conclusions are suggested by these figures, even though the numbers of cases and examinations are small. If inability to utilize starch is shown by its appearance in the stool to excess, by the presence of *Clostridia* and by the formation of gas, then it is relatively uncommon among patients suffering from ordinary chronic or acute disease. It occurs frequently enough, however, to give rise to the speculation that it may occur rather easily from slight causes and may clear up readily when these causes are removed. However, inability to utilize starch is found in the great majority of patients with chronic arthritis, and responds sluggishly to treatment. It would seem to be a definite disorder in these patients, since it does not react quickly to the amount or type of carbohydrate in the diet.

The significance of this observation is not apparent. Much work remains to be done to verify and explain it. Possibly it may point to an abnormal condition of the intestinal mucosa comparable to that of other tissues in the body in arthritis. In animals McCarrison [4] produced organic changes in the intestines and elsewhere by feeding diets deficient in vitamins and high in starch. By roentgen examination and barium enema Fletcher [5] found a decrease in haustral markings, loss of tone and lengthening of the colon in his arthritic patients whose nutrition

4. McCarrison, R.: Brit. M. J. **2**:730, 1926.

5. Fletcher, A. A., and Graham, D.: Am. J. M. Sc. **179**:91, 1930.

had been faulty for a long time, and he felt that this was evidence that the experimental observations held true for man. Our results tend to support his views.

SUMMARY

1. One hundred and forty-two stools from forty patients with chronic arthritis were analyzed in a simple routine way, and the results were compared with those obtained on examination of ninety-seven stools from seventy-one patients suffering from various other diseases.

2. No definite pathologic condition was found, except for the presence of starch in the stools from the arthritic group of patients. (*a*) Seventy-nine per cent of the stools showed an excess of starch, as compared with 26.8 per cent for the control group. (*b*) Iodine-staining organisms were found in the stools of 90 per cent of the patients, as compared to 22 per cent for the controls. (*c*) The fermentation test was positive in 82.5 per cent of the cases, as compared to 24 per cent for the controls.

3. Difficulty in the utilization of starch, while occasionally found in a variety of conditions, is prone to occur in patients with chronic arthritis, and adds further evidence that diets low in starch are of use in this disease.

THE TREATMENT OF PERNICIOUS ANEMIA WITH DESICCATED HOG'S STOMACH*

PROF. I. SNAPPER, M.D.
AND
J. D. G. DU PREEZ, M.D.
AMSTERDAM, HOLLAND

Since Cahn and von Mehring, in 1886, first drew attention to the absence of hydrochloric acid in a case of pernicious anemia, it has gradually become recognized that this association is practically a conditio sine qua non.

On the continent of Europe this subject has been investigated chiefly by Faber, Ewald, Zadek, Weinberg and others, Faber expressing as his opinion that achylia gastrica is generally preceded by a chronic gastritis. In England Hurst was the chief exponent; he also showed by means of the fractional test meal that the absence of free hydrochloric acid in pernicious anemia invariably persists throughout the whole period of digestion, whereas in other conditions, such as cancer of the stomach, it is not uncommon to find a small quantity of free acid in one or more of the fractions.

The significance of this achylia was pointed out by Castle,[1] who in a series of experiments with normal gastric juice and beef muscle, administered in different ways to patients with pernicious anemia, endeavored to establish an etiologic relationship between achylia gastrica and pernicious anemia. This constant achylia and the facts concerning the familial occurrence of pernicious anemia, as well as the frequency of achylia among relatives of patients suffering from this disease, constituted the fundamental thoughts that gave him the impetus to these experiments.

The work of Castle was the principal inducement to Sharp,[2] Sturgis and Isaacs,[3] and Conner [4] to treat patients for pernicious anemia by feeding them raw and desiccated hog's stomach. These workers came to the conclusion that stomach tissue per gram of fresh material is even

* Submitted for publication, Aug. 21, 1930.

1. Castle: Brit. M. J. **1**:1120, 1929; Am. J. M. Sc. **178**:748, 1929. Castle and Townsend: Ibid. **178**:764, 1929.

2. Sharp, E. H.: Antianemic Factor in Desiccated Stomach, J. A. M. A. **93**:749 (Sept. 7) 1929.

3. Sturgis, C. S., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. A. M. A. **93**:747 (Sept. 7) 1929.

4. Conner, H. M.: Treatment of Pernicious Anemia with Swine Stomach, J. A. M. A. **94**:388 (Feb. 8) 1930.

more active than liver, as a smaller amount of the former is required to induce a remission in the patient with pernicious anemia.

It was therefore considered necessary to carry out a series of experiments to verify this new treatment for pernicious anemia. If corroborated, this new method of treatment not only would be a medical discovery of great importance, but would replace the more expensive liver therapy.

We have thus far observed thirty patients treated with desiccated hog's stomach. For this purpose a Dutch pharmaceutical company placed their experimental supplies of desiccated hog's stomach at our disposal. The mode of preparation is as follows: The organs of

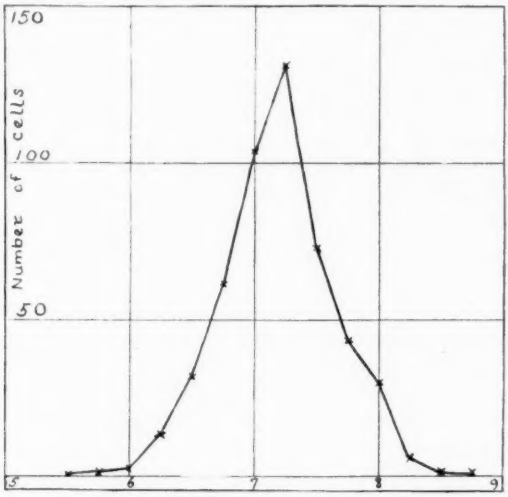

Chart 1.—Average Price-Jones curve of two normal persons; 500 cells in each instance.

healthy animals are taken from the body immediately after the slaughter and thoroughly and repeatedly washed in running water. The inside surfaces are then mechanically cleaned by means of a hard brush and the whole stomachs subsequently ground in a meat chopper to a fine pulp. The pulp is spread in thin layers on aluminum plates and placed in a special vacuum desiccator at temperatures ranging from 35 to 45 C. The organs dried by this method are then subjected to a process for the extraction of fat and finally pulverized.

The daily dosage varied from 3 to 6 spoonfuls (5 Gm.); it was usually administered before meals in lemonade or soup or mixed with porridge or other food.

Price-Jones' method of measuring the diameters of the red blood cells was employed in order to control the results of the treatment, as embodied in the appended charts; the megalocytosis and anisocytosis, as well as the improvement in the course of the treatment, are shown.

The influence of the administration of the stomach extract was controlled by reticulocyte counts; the reticulocytosis usually appeared about the fifth day after the treatment was started, and reached its maximum at about from the tenth to the twelfth day. The accompanying curves represent the number of reticulocytes per thousand erythrocytes, the number of red blood cells and the percentage of hemoglobin.

REPORT OF CASES

CASE 1.—J. H., a trader, aged 44, complained of lassitude and loss of energy for a year, so that he was unable to carry on his work. He had become pro-

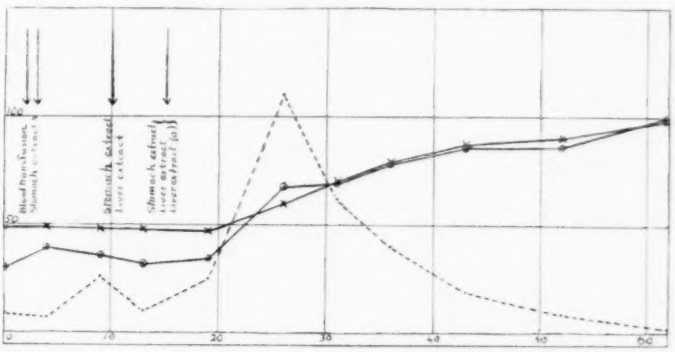

Chart 2 (case 1).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line). Liver extract (a) was given according to the method of Castle and Bowie.

gressively worse and had noticed that he was becoming paler and anemic. There were dyspnea on slight exertion and a history of much indigestion; however, there was no diarrhea. He also complained of soreness of the tongue. There was no tingling and numbness in the hands and feet. During the last month he had been treated with liver, with negative results.

Examination revealed pale yellow sclerae and a pale yellow skin; the teeth were carious; the tongue was smooth and atrophic. At the apex of the heart a slight systolic murmur was heard. The liver was not enlarged, and the spleen was just palpable. No other abnormalities were found.

Examination of the urine revealed no albumin or bilirubin; the test for urobilin was strongly positive. A blood count showed: hemoglobin, 48 per cent; erythrocytes, 2,010,000; color index, 1.2; white blood cells, 4,900; reticulocytes, 14 per thousand erythrocytes; platelets scanty; anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia; normoblasts and megaloblasts. The indirect van den Bergh test showed 20 mg. of bilirubin per liter of serum; the Was-

sermann test of the blood was negative. Fractional gastric analysis showed achylia. In the feces spectroscopic examination revealed no blood.

A tablespoonful of stomach extract was given four times a day. After a fortnight there was no improvement, and a transfusion of 500 cc. of blood was given. A week later, a liver extract was given four times a day in addition to the stomach extract. The patient did not react satisfactorily until he was also given liver extract according to the method of Castle and Bowie. Eleven days later, examination showed: hemoglobin, 60 per cent; erythrocytes, 3,400,000, and reticulocytes, 110 per thousand. Improvement was progressive, so that one month later the hemoglobin was 98 per cent and the erythrocytes numbered 5,000,000.

In this case it is difficult to state definitely what the essential part of the treatment was; it may have been the blood transfusion. We think that

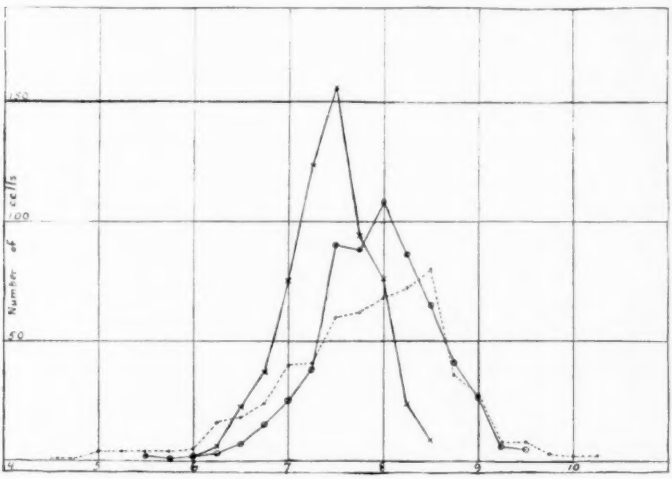

Chart 3 (case 1).—Price-Jones curves, each of 600 cells. On December 13 (dotted line) hemoglobin was 49 per cent and erythrocytes 1,510,000; on January 23 (circles), hemoglobin 87 per cent and erythrocytes 4,290,000; on February 18 (crosses), hemoglobin 98 per cent and erythrocytes 5,000,000.

the initial dosage of stomach extract was far too small for a severe case. The three Price-Jones curves (chart 3) clearly show how the blood picture became almost normal morphologically.

Case 2.—H. E., a woman, aged 66, engaged in housework, had been healthy until a year before examination, when she began complaining of weakness, lack of energy, pallor and tingling and numbness in the toes, so that she was unable to do her daily work. She also complained of pain in the tongue and palpitation of the heart on exertion. She had no diarrhea, but gave a history of occasional indigestion and slight edema of the ankles.

Examination revealed anemic conjunctivae; the sclerae were not jaundiced; the tongue was reddish and smooth, and the teeth were poor. The skin had a pale

yellowish tinge. No other abnormality was found, except that the liver was just palpable.

The urine contained a trace of albumin but no bilirubin; the test for urobilin, however, gave strongly positive results. A cytologic examination showed: hemoglobin, 50 per cent; red blood cells, 1,850,000; color index, 1.2; leukocytes, 4,100; reticulocytes, 2 per thousand; platelets, 60,000; poikilocytosis, anisocytosis and

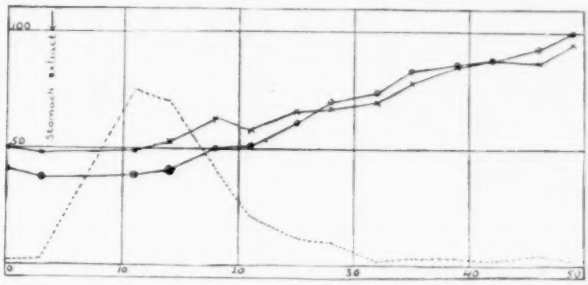

Chart 4 (case 2).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dotted line).

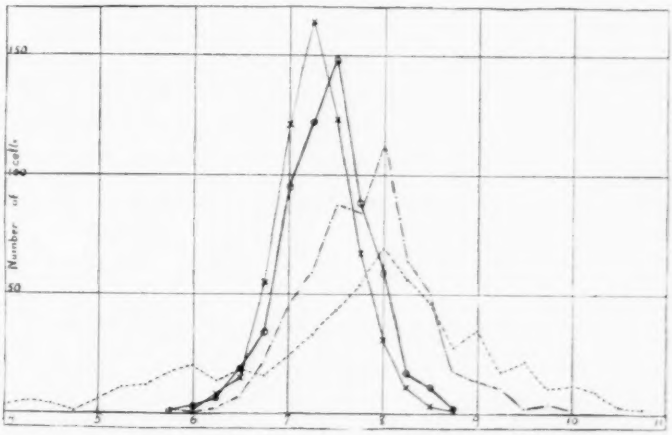

Chart 5 (case 2).—Price-Jones curves, each of 600 cells. On Nov. 14, 1929 (dotted line), erythrocytes were 1,850,000 and hemoglobin 50 per cent; on Jan. 3, 1930 (dot and dash), erythrocytes 4,500,000 and hemoglobin 95 per cent; circle line shows condition one month later; on June 26 (crosses), hemoglobin 100 per cent.

polychromatophilia; normoblasts but no megaloblasts. The direct van den Bergh test gave negative results; the indirect test showed 12 mg. of bilirubin per liter of serum. Fractional gastric analysis revealed no free hydrochloric acid; the

highest total acidity was 15. The blood pressure was 170 systolic and 75 diastolic; the Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood.

A tablespoonful of stomach extract was given three times a day. In about ten days the reticulocytes had increased to about 80 per thousand; at the same time

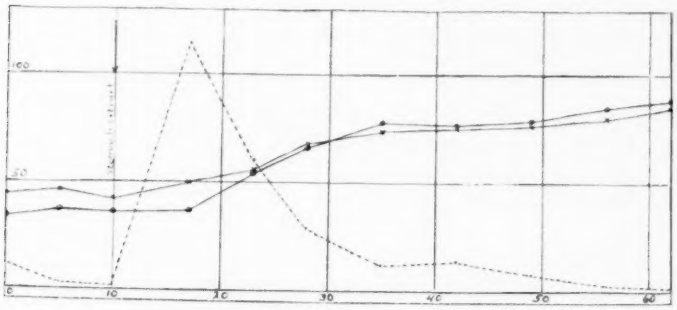

Chart 6 (case 3).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

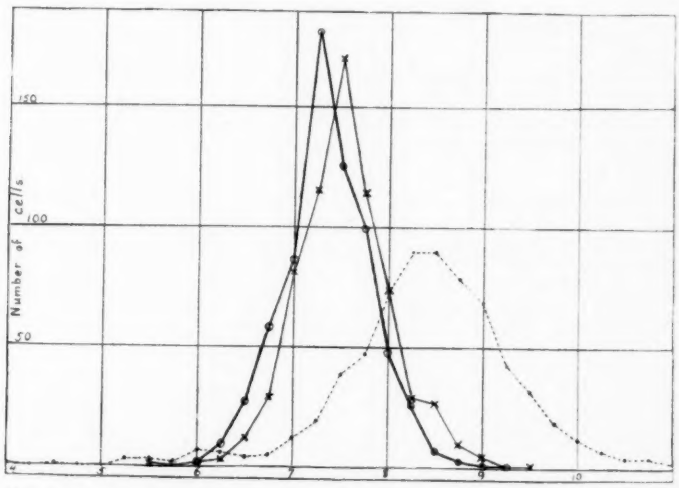

Chart 7 (case 3).—Price-Jones curves, each of 673 cells. On Dec. 7, 1929 (dotted line), erythrocytes were 1,610,000 and hemoglobin 44 per cent; on Feb. 5, 1930 (crosses), erythrocytes 4,400,000 and hemoglobin 85 per cent; four months later (circles), hemoglobin 102 per cent.

the hemoglobin and the number of red blood cells showed similar improvement, so that after treatment for forty-five days the blood picture showed: hemoglobin, 95 per cent; erythrocytes, 4,510,000, and the color index, 0.95.

In this case the use of stomach extract was a complete success, as is evidenced by the four Price-Jones curves (chart 5).

CASE 3.—J. T., a farmer, aged 64, complained of progressive loss of energy, dyspnea on exertion and general weakness. The skin had gradually become pale and yellowish. During the last few months preceding examination his legs had become stiff and walking difficult. He had no pain in the tongue, but often had a burning sensation in the mouth. The appetite was good; there was, however, a history of flatulence and indigestion, but no diarrhea.

On examination, the skin was a pale yellow; no cyanosis or dyspnea was present. The conjunctivae were anemic and the sclerae slightly jaundiced. The teeth were in a poor condition. Examination of the chest and abdomen revealed nothing abnormal. Definite medullary symptoms were present.

A test of the urine for urobilin gave strongly positive results. The blood count showed: hemoglobin, 44 per cent; erythrocytes, 1,610,000; color index, 1.3; leukocytes, 5,800; reticulocytes, 7 per thousand; anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia; normoblasts and a few megaloblasts. The Wassermann and Sachs-Georgi tests of the blood were negative. The indirect van den Bergh test showed 18.6 mg. of bilirubin per liter of serum.

A tablespoonful of stomach extract was given five times a day. After about seven days a strong reticulocytosis (114 per thousand) was observed. The improvement thereafter was progressive, the urobilin gradually disappearing from the urine. At the end of about fifty days the blood picture showed: hemoglobin, 85 per cent, and erythrocytes, 4,400,000.

In this case also the new treatment was successful. The Price-Jones curves (chart 7), made at the beginning and at the end of the treatment in the hospital and five months later, are among the best in this series. The symptoms in the spinal cord showed little or no improvement.

CASE 4.—J. R., a woman, aged 31, engaged in housework, enjoyed good health until about eight years before examination, when after the birth of a child she began complaining of general weakness and loss of energy. During the past year these complaints had become progressively worse, so that she was finally unable to do her housework. There was also soreness of the tongue, especially when she ate sour things.

Examination revealed carious teeth; the tongue was smooth and atrophic. The conjunctivae were anemic, while the sclerae had a touch of jaundice. Examination of the chest and abdomen revealed nothing abnormal, except that the liver was just palpable.

A test of the urine for urobilin was strongly positive. Examination of the blood showed: hemoglobin, 52 per cent; erythrocytes, 1,900,000; color index, 1.2; white blood cells, 4,100; reticulocytes, 6 per thousand; blood platelets scanty (82,000); anisocytosis, poikilocytosis and marked punctate basophilia; normoblasts and 2 megaloblasts. The indirect van den Bergh test showed 22.2 mg. of bilirubin per liter of serum. Fractional gastric analysis gave no free hydrochloric acid; the highest total acidity was 12. No blood was demonstrable in the feces spectroscopically or otherwise. The fundus was normal in both eyes. The Wassermann and Sachs-Georgi reactions were negative.

Treatment consisted of a tablespoonful of stomach extract three times a day, and dilute hydrochloric acid and pepsin. Within ten days the reticulocytosis

reached its maximum (140 per thousand). At the same time the hemoglobin and the red blood cell count began to improve, so that at the end of forty days the blood count showed: hemoglobin, 90 per cent; erythrocytes, 4,240,000, and color index, 0.95. The urine contained no urobilin. Fractional gastric analysis showed no free hydrochloric acid.

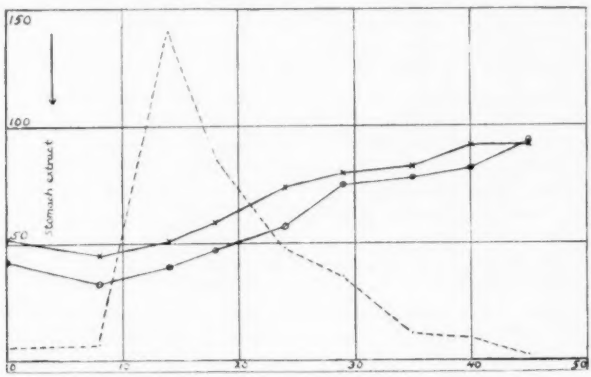

Chart 8 (case 4).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

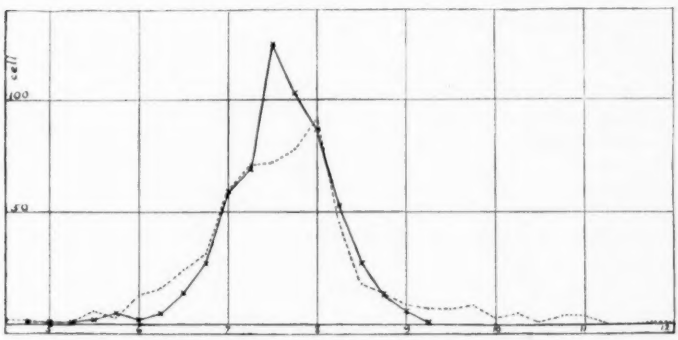

Chart 9 (case 4).—Price-Jones curves, each of 500 cells. On Dec. 4, 1929 (dotted line), erythrocytes were 1,900,000 and hemoglobin 52 per cent; on Jan. 18, 1930 (crosses), erythrocytes 4,240,000 and hemoglobin 90 per cent.

Case 5.—F. v. d. S., a woman, aged 56, engaged in housework, had been well until three years before examination, when she began to complain of general lassitude, loss of energy, vomiting and other symptoms of indigestion. She had pain in the tongue and ate poorly. She had become progressively paler and suffered from palpitation of the heart on the least exertion.

On examination, the conjunctivae appeared to be anemic; the sclerae had a yellowish tinge. There was no dyspnea or cyanosis. The teeth were artificial.

The tongue contained grooves in the middle and was smooth along the sides. The heart was enlarged two fingerbreadths to the left; systolic murmurs were heard at all ostia. The liver was palpable about three fingerbreadths from the costal margin; the spleen was just palpable.

The urine contained a trace of albumin; the test for bilirubin was negative and that for urobilin, strongly positive. Examination of the blood showed: hemo-

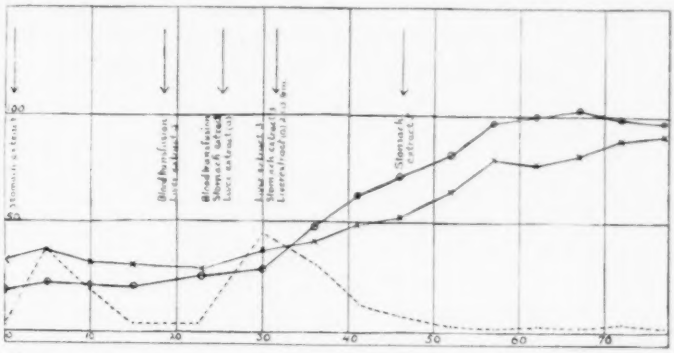

Chart 10 (case 5).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line). Liver extract (a) was made from 250 Gm. of fresh liver.

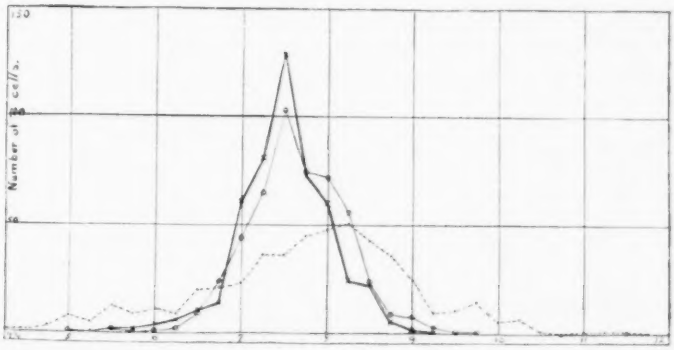

Chart 11 (case 5).—Price-Jones curves, each of 500 cells. On Dec. 22, 1929 (dash line), erythrocytes were 850,000 and hemoglobin 33 per cent; on Feb. 2, 1930 (circles), erythrocytes 4,390,000 and hemoglobin 90 per cent; on March 12 (crosses), erythrocytes 4,360,000 and hemoglobin 91 per cent.

globin, 33 per cent; erythrocytes, 850,000; color index, 1.6; leukocytes, 2,900; reticulocytes, 3 per thousand; blood platelets, 40,000; marked anisocytosis; poikilocytosis, polychromatophilia and punctate basophilia; several normoblasts and megaloblasts. The indirect van den Bergh test yielded 22 mg. of bilirubin per

liter of serum. The Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

Treatment consisted of a tablespoonful of stomach extract three times a day and dilute hydrochloric acid and pepsin. In three weeks the general condition of the patient had become worse and it was therefore decided to give a blood transfusion of 500 cc. The administration of stomach extract was stopped and instead liver extract was given, five times a day. Six days later, another blood transfusion of 500 cc. was given. Stomach extract was given three times a day in addition to the liver extract. Five days later there was a slight reticulocytosis (45 per thousand). It was decided, however, to add another liver extract, made from 250 Gm. of fresh liver. From then on there was decided improvement, so that fourteen days later the blood count showed: hemoglobin, 53 per cent, and erythrocytes, 3,280,000.

The liver extracts were removed from the treatment, the patient now being given only stomach extract, a spoonful five times a day. Improvement was continuous; a month later, the blood count was: hemoglobin, 91 per cent, and erythrocytes, 4,360,000.

In this case there is no doubt that the initial dosage of stomach extract (a tablespoonful three times a day) was far too small. The three Price-Jones curves (chart 11) illustrate the morphologic improvement in the red blood cells.

Case 6.—A. B., a housewife, aged 34, complained of weakness, lack of energy and pallor for two years. The onset of symptoms had been insidious, but they had become most pronounced eighteen months before examination, when the hemoglobin was only 15 per cent. She had pain in the tongue, but never suffered from diarrhea or from tingling and numbness in the fingers and toes. She was then residing in Germany and was treated with a liver preparation given for pernicious anemia. The hemoglobin content returned to 63 per cent. She continued to use the liver preparation, but after a few months her condition again became worse. A German preparation of desiccated hog's stomach caused some improvement, but later the condition became progressively worse.

On examination, the skin was a lemon yellow; the sclerae were slightly jaundiced; the conjunctivae showed extreme anemia. The teeth were carious. The tongue was smooth and atrophic. Examination of the chest revealed anemic murmurs at all ostia; otherwise observations were normal. The liver and spleen were both just palpable.

A test of the urine for urobilin gave strongly positive results. Examination of the blood showed: hemoglobin, 38 per cent; erythrocytes, 1,900,000; color index, 0.9; leukocytes, 2,600; reticulocytes, 6 per thousand; marked anisocytosis; poikilocytosis, punctate basophilia and polychromatophilia; many normoblasts and a few megaloblasts; platelets scanty. The direct van den Bergh test gave negative results; the indirect test showed 9 mg. of bilirubin per liter of serum. The Wassermann reaction of the blood was negative. No blood was demonstrable in the feces spectroscopically or otherwise.

Treatment consisted of a tablespoonful of stomach extract given six times a day, and dilute hydrochloric acid and pepsin. Twelve days later there was a strong reticulocytosis (204 per thousand). The improvement was progressive, so that after about fifty-three days the hemoglobin was 90 per cent and the erythrocytes numbered 4,750,000.

The color index was never greater than 1, nor was the Price-Jones curve (chart 13) typical at the beginning. Improvement under the administration of hog's stomach was no less striking, however, than in the other cases.

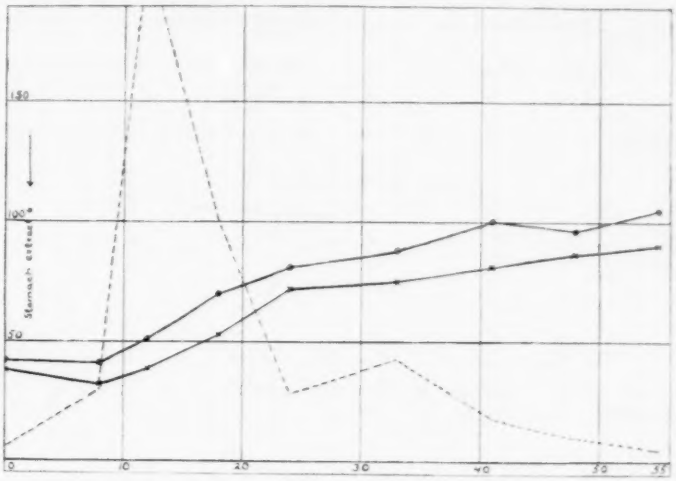

Chart 12 (case 6).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

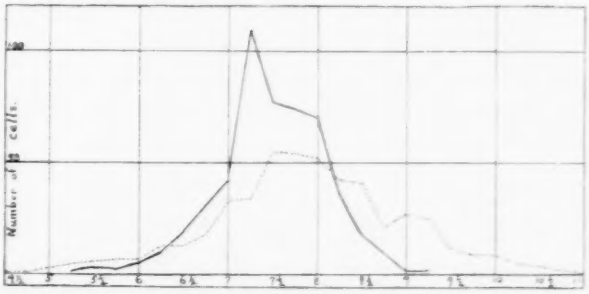

Chart 13 (case 6).—Price-Jones curves, each of 500 cells. On March 8, 1930 (solid line), erythrocytes were 1,900,000 and hemoglobin 38 per cent; on May 2 (dotted line), erythrocytes 4,570,000 and hemoglobin 90 per cent.

Case 7.—J. P., a printer, aged 62, was healthy until two years before examination, when he started to complain of grooves in the tongue which caused him much pain. Thereafter he began to complain of weakness; he got up tired and went to bed tired, so that at last he was unable to remain at his work. A year

before, he underwent treatment with liver, and the hemoglobin percentage rose from 30 to 80. Liver therapy was then discontinued, and twelve weeks later his condition was as poor as before.

On examination, the skin was of a lemon-yellow color; the conjunctivae were anemic. The tongue showed deep grooves in the middle, and was smooth along the sides. The teeth were poor. Examination of the chest and abdomen revealed nothing abnormal, except that both the liver and the spleen were just palpable.

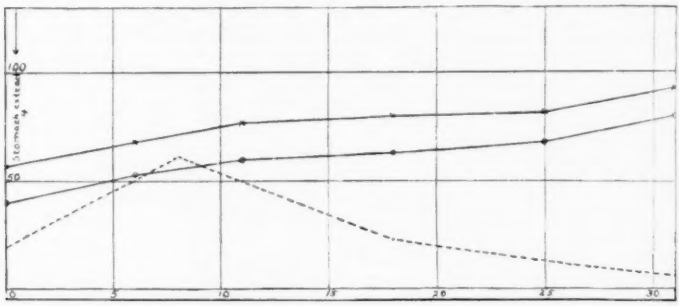

Chart 14 (case 7).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

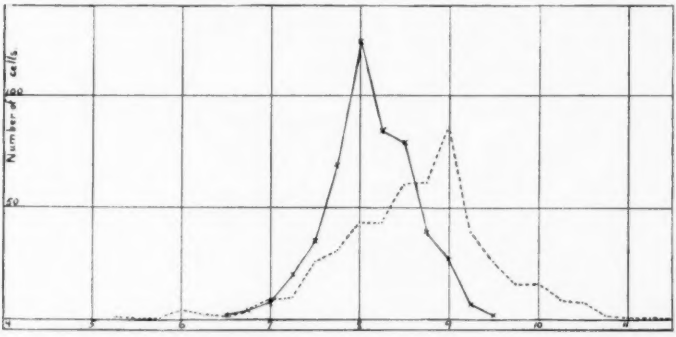

Chart 15 (case 7).—Price-Jones curves, each of 500 cells. On April 6, 1930 (dotted line), erythrocytes were 2,000,000 and hemoglobin 57 per cent; on May 7 (crosses), erythrocytes 4,020,000 and hemoglobin 93 per cent.

A test of the urine for urobilin gave strongly positive results. The blood picture showed: hemoglobin, 57 per cent; erythrocytes, 2,000,000; color index, 1.4; leukocytes, 4,900; reticulocytes, 19 per thousand; anisocytosis, poikilocytosis and polychromatophilia; 1 megaloblast and several normoblasts; blood platelets clearly diminished.

A tablespoonful of stomach extract was given four times a day. Between the sixth and eleventh days a reticulocytosis of about 60 per thousand was found;

the general condition improved so that, after a month's treatment, the hemoglobin was 93 per cent and the red blood count, 4,020,000.

Case 8.—T. V., a man, aged 56, had complained of weakness, loss of energy and palpitation of the heart for three and a half years. At the onset of the condition he began to look pale and lost considerable weight. He was sent to the south of France, and while there was treated with liver. Thereafter he was again able to do his work. Gradually, however, his condition became worse and

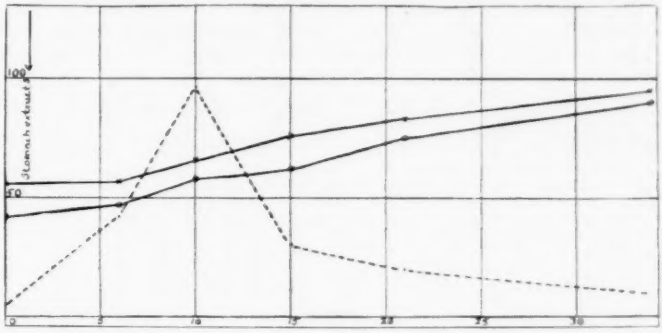

Chart 16 (case 8).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

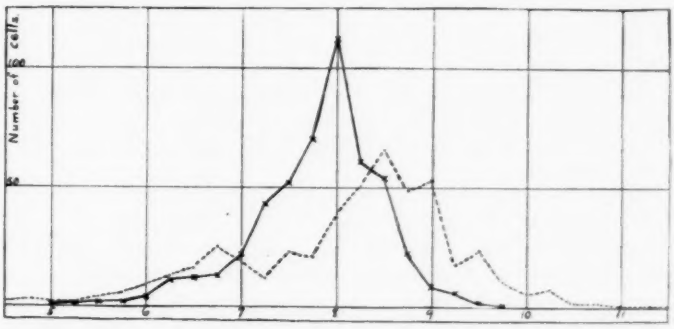

Chart 17 (case 8).—Price-Jones curves, each of 500 cells. On April 2, 1930 (dash line), erythrocytes were 2,000,000 and hemoglobin 56 per cent; on May 6 (crosses), erythrocytes 4,400,000 and hemoglobin 95 per cent.

diarrhea developed. He was again treated with liver and for a year he was able to attend to his work. Thereafter liver therapy was ineffective. He became progressively worse, had pain in the tongue and complained of tingling and numbness in the fingers.

On examination, the skin was of a lemon-yellow color. The conjunctivae were anemic; the sclerae were not jaundiced. The teeth were poor, and the

tongue smooth and atrophic. Further examination of the chest and abdomen revealed a palpable liver and spleen.

The urine contained no bilirubin; the test for urobilin was strongly positive. Examination of the blood showed: hemoglobin, 56 per cent; erythrocytes, 2,000,000; color index, 1.3; leukocytes, 4,700; reticulocytes, 4 per thousand; anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia; several normoblasts. No blood was found in the feces.

A tablespoonful of stomach extract was given five times a day. Ten days after the treatment was begun, the reticulocytosis had reached its maximum (96 per thousand). The patient's condition continued to improve generally, so that after thirty-five days, examination of the blood revealed: hemoglobin, 95 per cent, and erythrocytes, 4,400,000.

The morphologic improvement is evidenced by the Price-Jones curves at the beginning and at the end of the treatment (chart 17). It will be

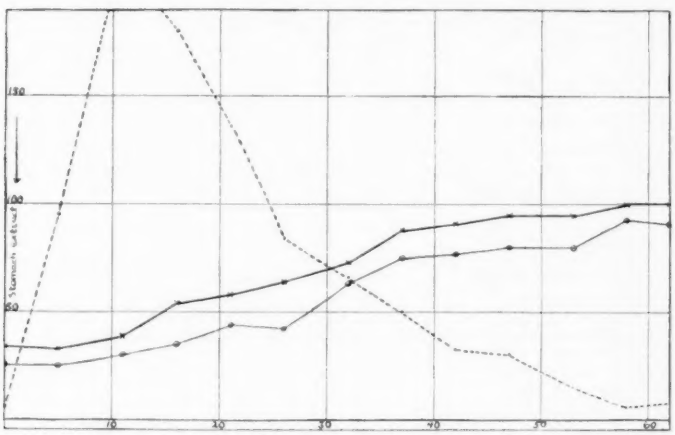

Chart 18 (case 9).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

noticed, however, that there still existed considerable megalocytosis, a condition that evidently does not run parallel with improvement in hemoglobin and red blood count.

Case 9.—G. B., a woman, aged 59, engaged in housework, complained of weakness in the legs and general lassitude for eight months. The last few months before examination her condition became much worse and she began to look pale. There was a history of indigestion and occasional vomiting. There was no soreness of the tongue or any unusual feeling in the hands or feet.

On examination, the skin showed a lemon-yellow pallor. The conjunctivae were anemic and the sclerae slightly jaundiced. The tongue was not smooth; the teeth were in a poor condition. The area of cardiac dulness was somewhat enlarged in both directions; systolic murmurs were heard at all ostia. Further examination of the chest, abdomen and extremities showed nothing abnormal.

The urine contained a trace of albumin but no bilirubin; tests for urobilin gave strongly positive results. Examination of the blood showed: hemoglobin, 34 per cent; erythrocytes, 1,160,000; color index, 1.3; white blood cells, 3,000; reticulocytes, 9 per thousand; platelets, 80,000; marked anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia; several normoblasts and 3 megaloblasts in 100 white blood cells. The direct van den Bergh test gave negative results; the indirect test showed 11.2 mg. of bilirubin per liter of serum. The blood pressure was 150 systolic and 60 diastolic. The Wassermann and Sachs-Georgi tests of the blood were negative. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

A tablespoonful of stomach extract was given six times a day. A marked reticulocytosis (215 per thousand) was noted about the eleventh day. From then on, the hemoglobin percentage and red blood count gradually improved, so that, after treatment for two months, examination showed: hemoglobin, 100 per cent, and erythrocytes, 4,100,000. Fractional gastric analysis with histamine revealed no free hydrochloric acid.

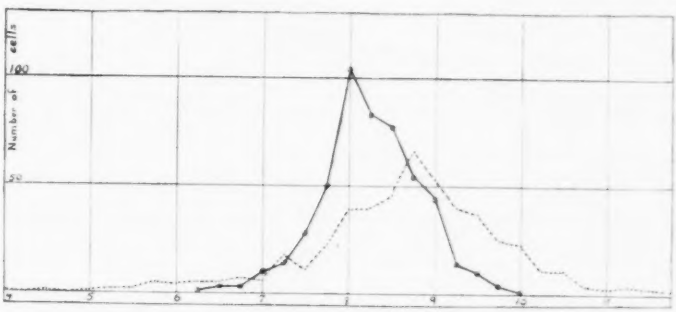

Chart 19 (case 9).—Price-Jones curves, each of 500 cells. On March 27, 1930 (dotted line), erythrocytes were 1,160,000 and hemoglobin 34 per cent; on May 19 (circles), erythrocytes 3,560,000 and hemoglobin 95 per cent.

CASE 10.—Z. T., a woman, aged 56, complained of tiredness and loss of energy for two years. Six months before examination, her condition became much worse; she looked pale and complained of palpitation and pain in the chest on the least exertion. She also complained of pain in the tongue and tingling and numbness in the hands and feet; she did not have diarrhea.

On examination, the skin was pale and yellowish; the conjunctivae were anemic and the sclerae slightly jaundiced. The teeth were in a poor condition and the tongue was smooth. The area of cardiac dulness showed a slight increase to the left; systolic murmurs were heard at the various ostia.

The urine contained a trace of albumin; tests for urobilin were strongly positive. Examination of the blood showed: hemoglobin, 32 per cent; erythrocytes, 1,350,000; color index, 1.1; white blood cells, 3,700; reticulocytes, 25 per thousand; marked anisocytosis and poikilocytosis; polychromatophilia and punctate basophilia; 6 normoblasts and 2 megaloblasts in 100 white cells; blood platelets definitely diminished. The direct van den Bergh test yielded negative results; the indirect test gave 16 mg. of bilirubin per liter of serum. The Wassermann and Sachs-Georgi tests were negative. The feces contained no blood. Fractional

gastric analysis revealed no free hydrochloric acid; the highest total acidity was 27.

A spoonful of stomach extract was given six times a day. The maximum reticulocytosis was reached about ten days after the treatment was begun; after thirty days' treatment, cytologic examination showed: hemoglobin, 80 per cent,

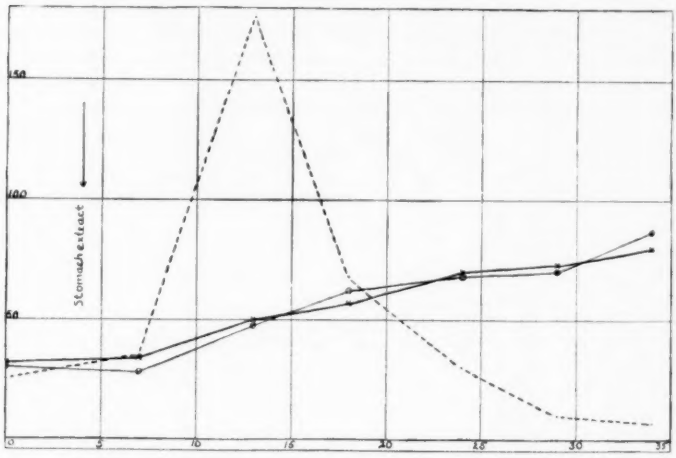

Chart 20 (case 10).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

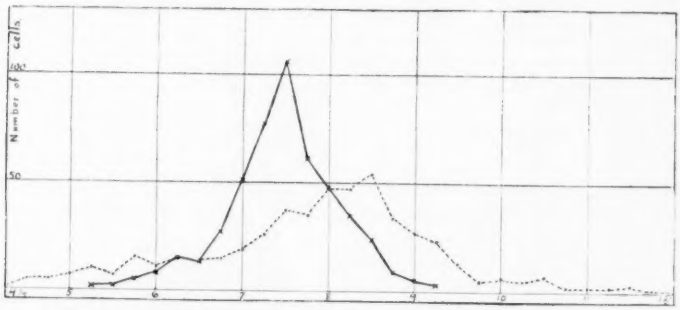

Chart 21 (case 10).—Price-Jones curves, each of 500 cells. On April 25, 1930 (dotted line), erythrocytes were 1,350,000 and hemoglobin 32 per cent; on May 30 (crosses), erythrocytes 3,910,000 and hemoglobin 80 per cent.

and erythrocytes, 3,910,000. The Price-Jones curves (chart 21) show a remarkable improvement in the megalocytosis.

Case 11.—M. S., a woman, aged 71, was well until fourteen months before examination, when she began to complain of lassitude and loss of energy. She was then treated with liver and remained well for seven months; then she was again

given liver, but unsuccessfully. She was discharged from the hospital in forty days with a hemoglobin percentage of only 34. Since then she had been bedridden.

On examination, the skin was a lemon-yellow color; no cyanosis or dyspnea was present. The conjunctivae were extremely anemic. The teeth were in a poor condition; the tongue was smooth and atrophic. The area of cardiac dulness was

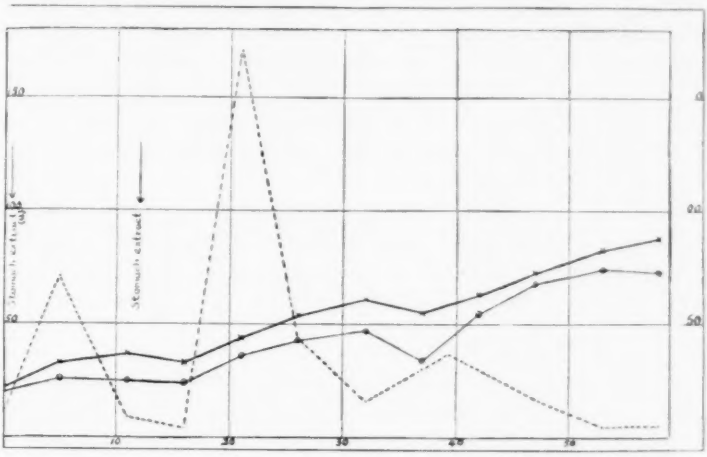

Chart 22 (case 11).—Course of hemoglobin content (crosses), red blood count (circles) and reticulocytosis (dash line).

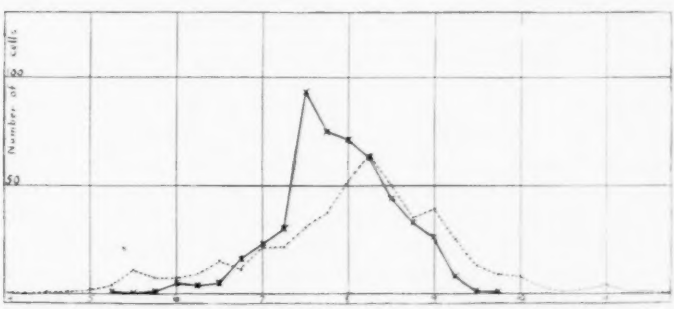

Chart 23 (case 11).—Price-Jones curves, each of 500 cells. On April 3, 1930 (dotted line), erythrocytes were 900,000 and hemoglobin 22 per cent; on May 31 (crosses), erythrocytes 3,260,000 and hemoglobin 88 per cent.

normal; systolic murmurs were heard at all ostia. Râles were heard over the left lower lung posteriorly. The liver and spleen were not palpable.

The urine contained a trace of albumin; tests for urobilin gave strongly positive results. Examination of the blood showed: hemoglobin, 22 per cent; erythrocytes, 900,000; color index, 1.1; leukocytes, 3,400; reticulocytes, 10 per thousand;

marked poikilocytosis and anisocytosis; polychromatophilia and punctate basophilia; 2 megaloblasts and several normoblasts in 100 white cells; a few blood platelets. The direct van den Bergh test gave negative results; the indirect test yielded 22 mg. of bilirubin per liter of serum. The Wassermann and Sachs-Georgi tests of the blood gave negative results. The feces contained no blood. Fractional gastric analysis revealed no free hydrochloric acid.

A German preparation of desiccated hog's stomach was given, 2 tablets four times a day. There was a slight reticulocytosis on about the fifth day, but as there was no general improvement, the German preparation was replaced by the stomach extract used in the previous cases, a tablespoonful a day, with the gratifying result that ten days later, the reticulocytosis reached a much higher level (172 per thousand). From then on there was a steady general improvement; at the end of fifty days' treatment with the second stomach extract the hemoglobin was 88 per cent and the erythrocytes were 3,260,000.

This was a great success for the stomach therapy. The condition of the patient was extremely poor and the prognosis doubtful considering her age, the hypostasis of the lungs, the extreme emaciation and the fact that liver therapy had been unsuccessful on a prior occasion.

COMMENT

It is interesting to note that the return of the red blood cells to normal size generally lagged behind the improvement in the percentage of hemoglobin, the red blood count, etc. In cases 2 and 3 it was possible to measure the diameters of the red blood cells five and four months, respectively, after the patient's discharge from the hospital, and it was found that the morphologic recovery had become complete. Minot and Medearis [5] studied the diameter of the red blood cells in patients treated with liver and came to a somewhat similar conclusion.

Since the beginning of these experiments and after our provisional report [6] of the first five cases, several workers have published their experiences on this subject. Wilkinson,[7] in England, successfully treated four patients with raw hog's stomach and two patients with desiccated stomach. He also showed that both the muscularis and the mucosa are active. Renshaw,[8] in the same country, succeeded with this treatment in a case that had proved refractory to liver. Hitzenberger,[9] of Vienna, reported one case and Rosenow,[10] of Berlin, two cases, in which treatment with desiccated hog's stomach was successful. Recently Meulengracht and Hecht-Johansen,[11] of Copenhagen, reported four

5. Minot and Medearis: J. Clin. Investigation **3**:541 (Feb. 20) 1927.
6. Snapper, I., and du Preez, J. D. G.: Nederl. tijdschr. v. geneesk. **74**:745 (Feb. 15) 1930.
7. Wilkinson: Brit. M. J. **1**:236 (Feb. 8) 1930.
8. Renshaw: Brit. M. J. **1**:334 (Feb. 22) 1930.
9. Hitzenberger: Wien. klin. Wchnschr. **43**:367, 1930.
10. Rosenow: Klin. Wchnschr. **9**:652 (April 5) 1930.
11. Meulengracht and Hecht-Johansen: Klin. Wchnschr. **9**:1162 (June 21) 1930.

cases in which pulverized desiccated hog's stomach, and two cases in which a stomach extract, was used.

Treatment for pernicious anemia with hog's stomach has therefore been established beyond all doubt. The consequences must be great, both theoretically and practically. Cases refractory to treatment with liver, especially with liver extracts, are not rare; besides, hog's stomach is a cheap article and, if equally active as a blood-maturing agent, will supersede the more expensive liver preparations and so bring a good and effective treatment within the reach of the general public.

CARBOHYDRATE METABOLISM IN HYPERTENSION*

MAX WISHNOFSKY, M.D.
AND
CHARLES S. BYRON, M.D.
BROOKLYN

It has been noted by clinical observers that a disturbance of carbohydrate metabolism exists in hypertension.

In 1910, Neubauer [1] observed the association of hyperglycemia in nephritis with hypertension, and postulated that an overactivity of the suprarenal glands was the causative factor. Hagelberg [2] made the same observation and accepted Neubauer's theory. Tachau [3] also concurred in these observations, but did not attempt to explain the mechanism involved. Bing and Jakobsen [4] were of the opinion that the hyperglycemia in all cases of hypertension with nephritis could be explained by a complicating condition such as dyspnea, uremia or a cerebral accident.

Hopkins [5] also observed hyperglycemia in hypertension with nephritis. Hamman and Hirschman [6] found that cases of high blood pressure, especially when complicated by nephritis, showed a so-called "diabetic" blood sugar curve after the administration of dextrose. Hirsch [7] noted that in the majority of cases of vascular hypertension without nephritis there was hyperglycemia and an abnormal rise in blood sugar after the taking of dextrose. Herrick [8] concurred in the opinion that high blood

* Submitted for publication, Sept. 22, 1930.

* From the Department of Metabolism and Pathology and the Medical Clinic (Service of Dr. S. R. Blatteis) of the Jewish Hospital.

1. Neubauer, E.: Ueber Hyperglykämie bei Hochdrucknephritis, Biochem. Ztschr. **25**:284, 1910.

2. Hagelberg, M.: Hypertonie und Blutzucker, Berl. klin. Wchnschr. **40**: 1877, 1912.

3. Tachau, H.: Eine neue Methode der Bestimmung des Blutzuckergehaltes, Deutsches Arch. f. klin. Med. **102**:597, 1911.

4. Bing, H. J., and Jakobsen, B.: Blutzucker Untersuchungen unter normalen und einigen pathologischen Verhältnissen, Deutsches Arch. f. klin. Med. **113**:571, 1913.

5. Hopkins, A. H.: Studies in Concentration of Blood Sugar in Health and Disease, Am. J. M. Sc. **149**:254, 1915.

6. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, Arch. Int. Med. **20**:761 (Nov.) 1917.

7. Hirsch, E.: Blutzucker und vasculäre Hypertonie, Biochem. Ztschr. **75**: 189, 1916.

8. Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**: 1942 (Dec. 8) 1923.

sugar occurred in cases of high blood pressure, more often when it was not associated with obvious disease of the kidney.

Kahler [9] found hyperglycemia in essential hypertension and believed that the possibility of the existence of sclerosis of the pancreatic blood vessels should be considered. Fahr [10] also postulated that the high blood sugar in cases of high blood pressure might be the result of a diminution in the output of insulin engendered by a sclerosis of the blood vessels of the pancreas. O'Hare [11] observed that a large number of cases of hypertension showed a high blood sugar curve after the ingestion of dextrose, and he believed that many of the patients were potentially diabetic.

Hitzenberger and Richter-Quittner [12] revived the theory of Neubauer. They stated that in both primary and secondary hypertension, hyperglycemia and elevation of the renal threshold for dextrose were present. The condition of hyperglycemia, hypertension and elevation of the renal threshold can be produced by the injection of epinephrine. Therefore, they urged that the entire complex could be explained by an increase in secretion by the suprarenals.

Only two observers reported contradictory observations. Knoopman [13] found high blood sugar in hypertension to be exceptional. Iwai and Löwy [14] noted that the blood sugar level during fasting and the blood sugar curve after the ingestion of dextrose were essentially normal in cases of high blood pressure.

Of interest in relation to this subject are the observations of Punschel [15] and of Spence.[16] They observed that in senility the blood sugar value during fasting and the dextrose tolerance curve were much higher than in young people.

It seems to be fairly definitely established, then, that in hypertension, whether or not complications such as nephritis exist, there is a

9. Kahler, H.: Zur Pathogenese der essentiellen Hypertonie, Wien. Arch. f. inn. Med. **3**:129, 1922.

10. Fahr, G.: Kurzer Beitrag zur Frage der Hypertonie, Berl. klin. Wchnschr. **58**:730, 1921.

11. O'Hare, J. P.: Glucose Tolerance Test in Chronic Vascular Hypertension, Am. J. M. Sc. **160**:366, 1920.

12. Hitzenberger, K., and Richter-Quittner, M.: Ein Beitrag zum Stoffwechsel bei der vaskulären Hypertonie, Wien. Arch. f. inn. Med. **2**:189, 1921.

13. Knoopman, J.: Blood Pressure and Sugar Metabolism, Endocrinology **8**: 340, 1924.

14. Iwai, S., and Löwy, F. E.: Zur Frage der Hyperglykämie bei Hochdruck, Klin. Wchnschr. **3**:1440, 1924.

15. Punschel, A.: Der Blutzucker im höheren Lebensalter unter besonderer Berücksichtigung der alimentären Hyperglykämie, Ztschr. f. klin. Med. **96**:253, 1923.

16. Spence, J. C.: Some Observations on Sugar Tolerance with Special Reference to Variation Found at Different Ages, Quart. J. Med. **14**:314, 1920-1921.

disturbance in the metabolism of carbohydrate. This may manifest itself as hyperglycemia and glycosuria. The more constant feature, however, is the exhibition of a high blood sugar curve on the administration of an adequate amount of dextrose.

The elucidation of the factors concerned in this disturbance is not simple. Fahr,[10] Kahler [9] and O'Hare [11] considered this condition to be the result of a diminution in the secretion of insulin engendered by sclerosis of the blood vessels of the pancreas; or, to put it more concretely, these cases are either potentially or mildly diabetic. Neubauer,[1] Hagelberg,[2] Tachau [8] and Hitzenberger and Richter-Quittner,[12] on the other hand, expressed the belief that the entire picture can be explained by the existence of a hyperadrenalemia.

The differences between these two conceptions are fundamental. In both conditions a "diabetic" blood sugar curve is obtained on the administration of dextrose. In diabetes mellitus the respiratory quotient curve is lower than normal after the ingestion of dextrose; in hypersuprarenalinemia, on the other hand, the curve is normal. This point is of cardinal importance because it helps separate diabetic from nondiabetic patients. Thus Linder, Hiller and Van Slyke [17] found that in nephritis, in which there may be a marked diminution in tolerance for dextrose, the respiratory quotient curve is normal. Similarly, Sanger and Hun [18] found this to be true in hyperthyroidism. We [19] suggested that a study of the respiratory quotient curve would serve to distinguish diabetic from nondiabetic cases in acromegaly, in which there is practically always a disturbance in carbohydrate metabolism.

At this point a few words may be said about the respiratory quotient curve. The respiratory quotient of normal persons twelve hours after a meal was determined by Benedict, Emmes, Roth and Smith [20] and found to be 0.83 for men and 0.81 for women. As a rule it is lower in diabetic patients; the more severe the diabetes, the lower is the quotient. The respiratory quotient during fasting will be lower in normal persons if they have been deprived of carbohydrates for several days. Conversely, it has been shown by Benedict, Emmes and Riche [21] that following an evening meal rich in carbohydrate, the respiratory quotient on

17. Linder, G. C.; Hiller, A., and Van Slyke, D. D.: Carbohydrate Metabolism in Nephritis, J. Clin. Investigation **1**:247, 1925.

18. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

19. Wishnofsky, M., and Byron, C. S.: Carbohydrate Metabolism in Acromegaly, J. Lab. & Clin. Med. **15**:216, 1929.

20. Benedict, F. G.; Emmes, L. E.; Roth, P., and Smith, H. M.: The Basal, Gaseous Metabolism of Normal Men and Women, J. Biol. Chem. **18**:139, 1914.

21. Benedict, F. G.; Emmes, L. E., and Riche, J. A.: The Influence of the Preceding Diet on the Respiratory Quotient After Active Digestion Has Ceased, Am. J. Physiol. **27**:383, 1911.

the following morning may be 0.88. It is seldom, however, that such marked changes in the diet are encountered as were employed by these experimenters with their subjects.

It has been shown by Bernstein and Falta [22] and others that after the administration of dextrose the respiratory quotient will not rise until an optimum percentage of glycogen is obtained in the liver. It is only after the glycogen depots have been filled that the oxidation of dextrose will commence. Consequently, in a person who has been on a diet poor in carbohydrate for several days, there will be a delay in the rise of the respiratory quotient, whereas when the body is surfeited with glycogen there will be an early rise which to some extent must be attributed to the conversion of carbohydrate into fat. Gigon [23] found that in a normal person the respiratory quotient never rises before one-half hour after the administration of dextrose. Indeed, Bornstein and Holm [24] found that it may actually fall during the first fifteen minutes, and they suggested that this may be due to carbon dioxide being retained in the body to combine with the alkali released by the secretion of acid in the gastric juice. The respiratory quotient is highest at the end of three hours, at which time the blood sugar is normal. The quotient during fasting is, as a rule, attained at the end of from four to six hours.

Ten cases of hypertension were investigated by us along these lines, namely, by a simultaneous study of the blood sugar and the respiratory quotient curves. These cases were chosen at random from the out-patient department. The ages of the patients ranged from 40 to 70 years. The lowest systolic blood pressure was 170 mm. of mercury; in most cases it was considerably above this. The patients were on normal diets previous to the day of the test. This point is of extreme importance, for, as mentioned, if the person is on a diet poor in carbohydrate for several days, an abnormally low curve for the respiratory quotient will result on the administration of dextrose. It has also been demonstrated that under similar conditions a "diabetic" blood sugar curve can be obtained in normal persons.

The question of standards of normal will now be considered. A normal blood sugar curve (venous blood) may be accepted as one that has a fasting level of from 0.8 to 0.11 per cent, that reaches its peak in one hour—as a rule much earlier—after the ingestion of dextrose, rarely going higher than 0.17 per cent, and that tends to regain its fasting level and frequently even a lower value within two hours, and occasionally in three hours. In two cases blood from the tips of the

22. Bernstein, S., and Falta, W.: Respiratorischer Stoffwechsel und Blutzucker Regulation, Deutsches Arch. f. klin. Med. **125**:233, 1918.

23. Gigon, quoted by Bornstein and Holm: Biochem. Ztschr. **130**:210, 1922.

24. Bornstein, A., and Holm, K.: Ueber den respiratorischen Stoffwechsel bei alimentärer Glykämie, Biochem. Ztschr. **130**:209, 1922.

finger was utilized, which has been shown by Foster [25] to be identical with that of arterial blood. For reasons that need not be discussed here, when arterial blood is used the blood sugar curve is higher than that for venous blood. According to Foster [25] and from our own experience, the figures of a normal blood sugar curve (arterial blood) are as follows: 0.10 per cent fasting level, and 0.21 and 0.12 per cent, three quarters of an hour and two hours after the ingestion of dextrose, respectively.

The respiratory quotient curves of Sanger and Hun [18] were accepted as standards of normal (table 1). Their normal subjects received 1.75 Gm. of dextrose per kilogram of body weight, which is the amount given to our patients with hypertension. Their figures are substantiated by the work of Bornstein and Holm.[24]

METHOD OF PROCEDURE

After having fasted for fourteen hours, each patient received 1.75 Gm. of dextrose per kilogram of body weight. Three specimens of blood were taken

TABLE 1.—*Curves of Respiratory Quotient in Normal Controls (Sanger and Hun)*

Name	Basal	30 Minutes*	60 Minutes	90 Minutes	120 Minutes	150 Minutes	Range
C. L.	0.78	0.82	0.80	0.89	0.87	0.94	0.16
H. D.	0.83	0.81	0.80	0.88	0.88	0.90	0.09
W. U. G.	0.75	0.84	0.88	0.88	0.84	0.90	0.15
E. H.	0.77	0.80	0.80	0.90	0.92	0.90	0.15
B. S.	0.78	0.80	0.84	0.86	0.88	0.86	0.10
M. C.	0.79	0.82	0.88	0.89	0.92	0.93	0.14
M. C.	0.83	0.83	0.86	0.83	0.92	0.90	0.09
H. J.	0.85	0.83	0.84	0.88	0.93	0.89	0.10
R. Mc.	0.83	0.88	0.84	0.88	0.93	0.92	0.10
H. R. Q.	0.75	0.79	0.81	0.86	0.83	0.87	0.12
Average	0.80	....	....	....	....	....	0.12

* 1.75 Gm. of dextrose per kilogram of body weight.

from each patient; one at the "fasting level," and two forty-five minutes and two hours after ingestion, respectively. The sugar content of the venous blood was determined by the Folin-Wu method, and that from the tip of the finger by the Kramer-Gittleman [26] micromethod. The respiratory quotient was determined at the "fasting level," and at one and one-fourth and t two and one-fourth hours after ingestion, respectively. These time intervals were chosen after careful consideration as best describing the nature of the curve. The gas was collected in a Tissot spirometer and analyzed by the method of Henderson and Haldane.

RESULTS

The results are incorporated in table 2. The blood sugar curves will be examined first. Accepting 0.11 per cent as the upper limit of normal, six of the ten patients had blood sugar values during fasting above normal. The ten patients had blood sugar curves above normal.

25. Foster, G. L.: Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, J. Biol. Chem. **55**:291, 1923.

26. Kramer, B., and Gittleman, I. F.: Technic for Quantitative Estimation of Sugar in Very Small Amounts of Blood, J. A. M. A. **81**:1171 (Oct. 6) 1923.

TABLE 2.—*Curves for Blood Sugar and Respiratory Quotient in Cases of Hypertension*

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8		Case 9*		Case 10*	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	118	0.73	91	0.75	102	0.80	115	0.70	111	0.79	133	0.75	96	0.72	81	....	151	0.81	148	0.79
45 minutes†	214		172		157		166		214		205		183		172		260		236	
75 minutes		0.83		0.80		0.88		0.88		0.92		0.856		0.83		0.89		0.92		0.88
120 minutes	100		145		191		191		172		187		140		138		210		214	
135 minutes		0.91		0.90		0.89		0.87		0.96		0.848		0.92		0.91		0.88		0.89

* In cases 9 and 10 blood was taken from the tip of the finger.

† The patients were given 1.75 Gm. of dextrose per kilogram of body weight.

After careful consideration of the figures of Sanger and Hun [18] and those of Bornstein and Holm,[24] it was decided that the respiratory quotient curve may be considered normal if its peak is 0.88 or more after the ingestion of 1.75 Gm. of dextrose per kilogram of body weight. According to this standard, all of the patients, except the one in case 6, had normal respiratory quotient curves. In case 6 the quotient rose only to 0.856. This patient also had the highest value for blood sugar during fasting, 0.133 per cent.

COMMENT

In diabetes mellitus there is a deficiency in glycogenesis and storage of glycogen. Whether or not there is also a diminution in the ability to oxidize dextrose is still in a polemic state. Macleod [27] stated, "The occurrence of these low quotients and their failure to respond to ingestion of glucose are often cited as evidence that the tissues in diabetes have lost the power to oxidize carbohydrate, but there is no direct evidence that this is really so." Joslin [28] expressed the belief that the diabetic patient can burn sugar if the sugar can first be transformed into glycogen. This may be accepted as incontrovertible: that in diabetes the respiratory quotient during fasting is lower than normal, and that the respiratory quotient curve fails to rise to a normal level after the ingestion of dextrose. A low curve for the respiratory quotient indicates a deficiency of insulin or a neutralization or inactivation of an adequate supply of insulin.[29] The converse is true; namely, that a normal respiratory quotient indicates an adequate secretion of insulin.

A large amount of work has been done on the use of the dextrose tolerance test in the diagnosis of diabetes mellitus. However, a so-called "diabetic curve" is obtained in so many conditions that this test must be considered inadequate. Far more information may be obtained by studying simultaneously the blood sugar and the respiratory quotient curves.

The various theories advanced to explain the disturbance in carbohydrate metabolism in hypertension will now be reconsidered. They are: (1) the existence of sclerosis of the blood vessels of the pancreas leading to a diminution in the secretion of insulin, and (2) the presence of a hyperadrenalemia.

---

27. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 6, St. Louis, C. V. Mosby Company, 1930, p. 912.

28. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 103.

29. This does not include phlorizin diabetes, in which the respiratory quotient rises only slightly after the administration of dextrose. This is the result, not of the inability of the organism to oxidize dextrose, but of the rapid elimination of dextrose by the kidney.

In nine of ten cases examined by us the respiratory quotient curve was normal after the ingestion of dextrose. This is definite evidence that there is an adequate secretion of insulin; that is, that diabetes mellitus does not exist. In the single case in which the respiratory quotient curve was lower than normal, the diagnosis of diabetes mellitus could be made, which condition is coexistent with and independent of the hypertension.

The injection of epinephrine gives rise to a "diabetic" blood sugar curve after the ingestion of dextrose. It was shown by Lusk [30] that if dextrose was given to normal dogs and then epinephrine was administered the respiratory quotient rose to unity, showing a normal combustion of carbohydrate. A hyperadrenalemia could then give rise to blood sugar and respiratory quotient curves as found by us.

In 1904, Vaquez [31] formulated the doctrine that hypertension is due to a hyperadrenalemia. Janeway [32] characterized this as a "beautiful dream." Broking and Trendelenburg [33] did not find an increase of epinephrine in the blood in hypertension. Stewart [34] stated that it is impossible to demonstrate epinephrine in human serum. It might be added that hyperplasia and adenoma of the suprarenal cortex are common in hypertension, but it is the medulla which secretes epinephrine, and changes are rarely found there.

In the present state of knowledge the theory that hyperadrenalemia causes the disturbance in carbohydrate metabolism cannot be proved.

When one considers the fact that in diabetes mellitus the explanation of the pathologic physiology is still in the stage of "theories," it is not strange that we should be in the dark about the mechanism concerned in the disturbance of carbohydrate metabolism in hypertension. Our object in performing this work was twofold: (1) to confirm that a disturbance of carbohydrate metabolism does exist, and (2) to determine its relation to diabetes mellitus. From our observations it can be deduced that a disturbance exists in all cases of hypertension that are not related to diabetes. Much more research of carbohydrate metabolism in general is necessary before we can hope to explain the pathologic physiology of this condition.

---

30. Lusk, G.: The Alleged Influence of the Adrenals on Diabetic Metabolism, Arch. Int. Med. **13**:673 (May) 1914.

31. Vaquez, quoted by Oppenheimer, B. S., and Fishberg, A. M.: Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

32. Janeway, T. C.: Nephritic Hypertension, Am. J. M. Sc. **145**:638, 1913.

33. Broking, E., and Trendelenburg, P.: Adrenalinnachweis und Adrenalingehalt des menschlichen Blutes, Deutsches Arch. f. klin. Med. **103**:163, 1911.

34. Stewart, G. N.: So-Called Biological Tests for Adrenalin in Blood, with Some Observations on Arterial Hypertonus, J. Exper. Med. **14**:377, 1911.

SUMMARY AND CONCLUSIONS

A dextrose tolerance test was performed on ten patients suffering from hypertension. The blood sugar and the respiratory quotient curves were studied simultaneously. In six of the ten cases the blood sugar during fasting was higher than normal. It was shown that all patients with hypertension have high blood sugar curves. The respiratory quotient curves were normal in nine of the ten cases. This is adequate proof that there is no diminution in the secretion of insulin in hypertension, and that these patients are neither potentially nor mildly diabetic. It disproves the theory that the disturbance in carbohydrate metabolism in hypertension is caused by sclerosis of the blood vessels of the pancreas. In the case in which the respiratory quotient curve was lower than normal, diabetes mellitus, independent of the hypertension, could be considered to exist.

The theory that hyperadrenalemia is the cause of the disturbance cannot be proved in the present state of knowledge.

The mechanism concerned in producing this disturbance in carbohydrate metabolism in hypertension is unknown and awaits further research for its elucidation.

PROGRESSIVE THROMBOSIS OF THE PULMONARY ARTERY *

CLARENCE H. BOSWELL, M.D.
AND
HAROLD D. PALMER, M.D.
ROCKFORD, ILL.

Although the fatal pulmonary thromboses usually follow major operations or are postpuerperal, yet purely medical thrombi do occur, and in the artery the latter are more frequently primary than embolic. The facts that the pulmonary artery functions as a vein and that the blood it conveys is more venous than that in any other vein lead it to the same thrombotic accidents to which veins elsewhere are subjected. Sepsis, anesthesia, atheromatous changes, stasis in the blood stream and low blood pressure all predispose to the formation of a thrombus, and the case reported here illustrates, we believe, such a combination of etiologic factors.

REPORT OF CASE

History.—A shop foreman, aged 39, entered Rockford Hospital on Oct. 20, 1929, complaining of a general sense of unrest, malaise, anorexia, palpitation, shortness of breath, easy fatigue and some aching through the chest. He had always been a hard worker. Four weeks prior to admittance, he had experienced an acute respiratory infection, consisting of congestion in the head and a mild cough. This lasted three or four days, and the patient dated the foregoing symptoms from this time. Eight months prior to the present illness, he had an attack of pain on defecation with explosive stools containing some blood and mucus. There were two or three stools a day during this attack, which lasted three weeks. Belching and flatulence after heavy meals persisted, but the stools became well formed, normal in number and contained no blood or mucus.

The father died of a stroke at the age of 63. The mother was living and well.

Examination.—The patient apparently was not seriously ill. The head, throat and neck were normal. The lungs were clear and resonant throughout; the cardiac rate was regular, and the heart was not enlarged; a soft systolic and diastolic murmur was heard at the apex.

There were no masses, tenderness or enlarged viscera in the abdomen. The lymph glands over the body were not enlarged, and the reflexes were normal. No foci of infection were found in the teeth, tonsils, sinuses or prostate.

Throughout the patient's stay in the hospital, his pulse rate ranged from 80 to 100, his temperature from 97 to 99 F., and his respiration from 20 to 30. The blood pressure was 108 systolic and 70 diastolic.

---

* Submitted for publication, Oct. 5, 1930.

* From the Departments of Internal Medicine and Pathology of Rockford Hospital.

A blood culture was sterile. The Kahn test was negative. The blood count revealed: hemoglobin, 88 per cent; red blood cells, 4,300,000; white blood cells, 11,350; polymorphonuclears, 57 per cent; eosinophils, 1 per cent; basophils, 1 per cent; lymphocytes, 36 per cent; large mononuclears, 4 per cent. The red blood corpuscles were normal in size, shape and staining.

Chemical and microscopic examination of the urine gave negative results. No blood, pus, parasites or ova were found in the stool. A roentgenogram of the

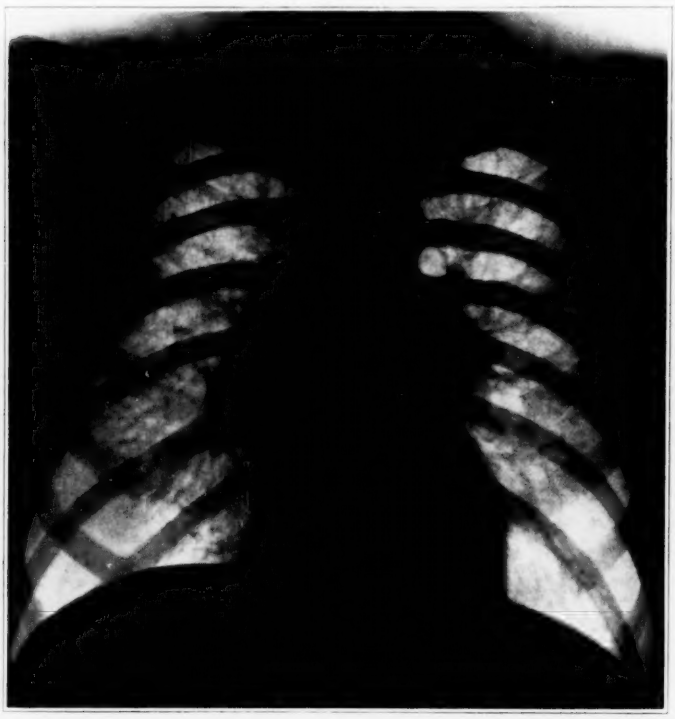

Fig. 1.—Roentgenogram showing the thrombus in the pulmonary artery on the right side.

chest showed increased density of the shadow of the right pulmonary artery, but its significance was not recognized before death.

Course.—After twenty-four hours in bed, the patient felt very comfortable, the pain in his chest and his general discomfort having subsided. On October 24, he was feeling better than at any time in the past two weeks. His heart was quiet; no murmurs or irregularities were heard, and there was no fever. As the blood culture was negative, the diagnosis of myocardial injury following the acute respiratory infection was thought probable.

On October 25, the patient had more dyspnea; the heart showed premature contractions, and a diastolic murmur returned.

On October 26, he had distress and gas in the upper part of the abdomen and passed a moderate amount of dark blood in the stool. This disappeared in twenty-four hours, and did not recur.

On October 29, after a good night's rest, the patient awoke and suddenly became dyspneic and cyanotic. This condition gradually progressed; his pulse became weaker, and he died late in the afternoon. He did not show the pallor of hemorrhage but cyanosis due to failure of the right side of the heart predominated.

Autopsy.—The peritoneal, pleural and pericardial cavities were normal. The heart weighed 360 Gm. The right auricle was somewhat dilated. The cardiac

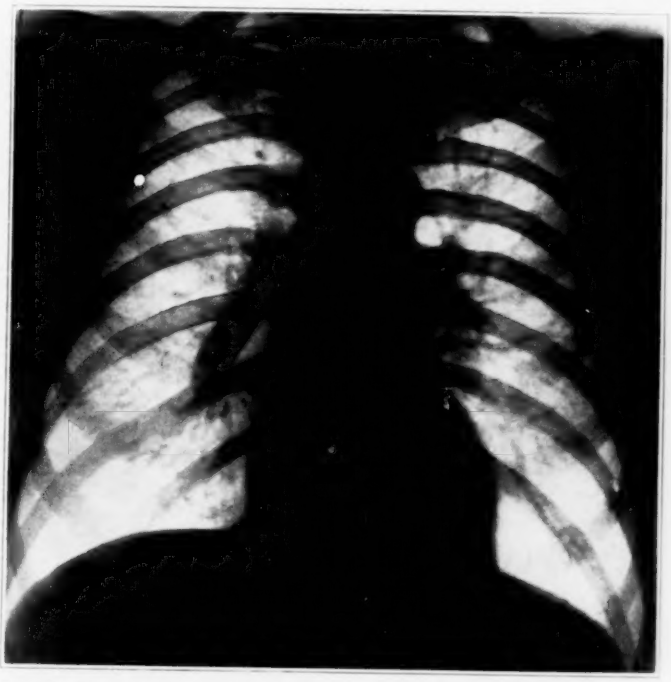

Fig. 2.—Print of the roentgenogram in figure 1 retouched to show the size and position of the thrombus.

muscle was reddish brown and firm, and the endocardium was smooth throughout. The valves were thin, delicate and smooth. The papillary muscles and chordae tendonae were normal. The coronary vessels were pliable and not occluded. The aortic arch was not dilated. There was no gross atherosclerosis.

The muscle cells were not hypertrophied. There were some fragmentation, indistinct striation and vacuolization of fibers under the endocardium. Several sections through the coronary vessels were entirely normal.

The intima of the whole aorta was smooth, with no gross atherosclerosis.

The lungs crepitated, and the cut surface showed no solid areas except for about 1 cm. of the peripheral portion of the right lung, which was apparently

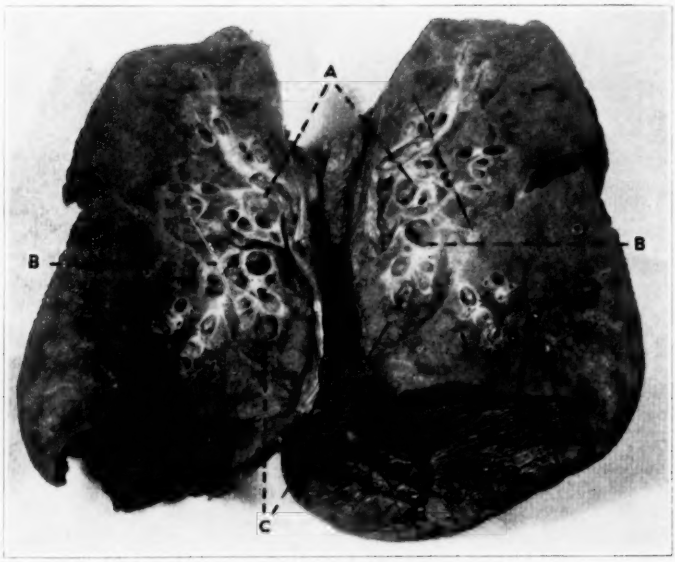

Fig. 3.—Photograph of the right lung sectioned through the hilus, showing the thrombi in the pulmonary artery and its branches. *A* indicates the main artery, completely occluded. Note that all but a small portion is an old thrombus. Note the demarcation (*B*) between old and new parts of the thrombus. The thrombus (*C*) here is old, but does not completely occlude the vessel.

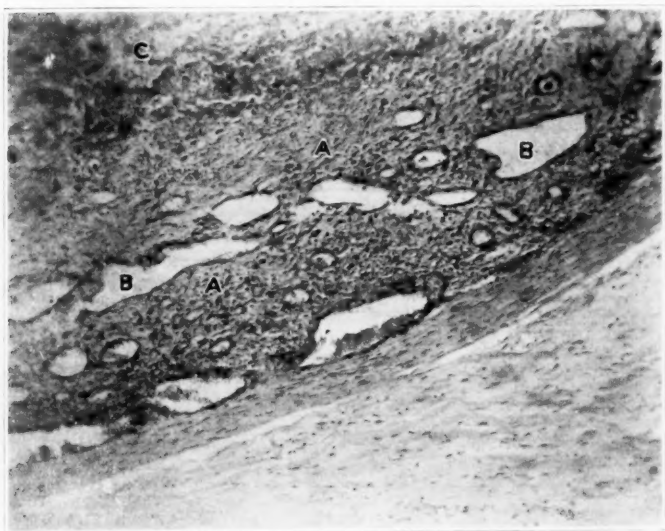

Fig. 4.—Photomicrograph through the wall of the pulmonary artery at the site of the older part of the thrombus. Note organization (*A*), canalization (*B*) and lamellated clot (*C*).

Fig. 5.—High power photomicrograph of the wall of the pulmonary artery showing acute inflammation. Note the polymorphonuclears.

Fig. 6.—Photomicrograph of a section taken at the periphery of the right lung. This whole area is the seat of hemorrhagic infarction.

solid and very bloody. The lung from this portion to the hilus was spongy and quite normal, except that in the hilus one found the pulmonary artery completely filled with a thrombus. All of this thrombus, except a small portion at one extremity, was old, gray and firmly fixed around the whole periphery. The newer portion was red. Immediately adjacent was the bronchus, and numerous lymph glands lay beside the branches of the pulmonary artery. The thrombus extended into the ramification of the artery, but some of the branches were not completely occluded. The left lung showed a similar condition, except that most of the thrombus was new. It was, however, definitely fast to the wall.

A microscopic section at the periphery of the lung showed an area from 3 to 5 mm. in depth (just beneath and including the pleural surface) to be the seat of recent hemorrhagic infarction. Sections through the pulmonary artery showed an old thrombus with advanced organization. The thrombus was firmly attached throughout nine tenths of its circumference. There was some canalization of the oldest portions. About one tenth of the thrombus was new.

The bronchus showed evidence of acute inflammation with polymorphonuclears very numerous just beneath the epithelium. The lymph glands were also chronically diseased, and there was a definite arteritis of the wall of the pulmonary artery where it was in contact with the lymph glands.

The liver, gastro-intestinal tract, spleen, suprarenals, kidneys, pelvic viscera and lymphatic structures were normal. The bone marrow, the organs of the neck, skull, sinuses and the spinal cord were not examined.

COMMENT

The patient had definite symptoms for some time prior to death, but these suddenly became aggravated and terminated fatally in a relatively short time. Postmortem examination revealed thrombo-arteritis of the pulmonary artery with complete occlusion. The thrombus was of some age, being well organized and in places canalized; though old, the thrombus became complete only during the last few hours, as is shown positively by the newer portions of the thrombus. The thrombus on the left side was much less extensive, and probably the result of right-sided retrogression. There was no evidence of chronic congestion, showing that the heart was competent up to the time of the last sudden occlusion.

Had we been able to interpret the roentgen evidence properly, our diagnosis would have been simplified.

We believe this to be a case of thrombo-arteritis, primary in the pulmonary artery and not embolic. The sequence of events may have been: (1) acute respiratory infection occurring five weeks before death resulting in (2) lymphadenitis and bronchitis; this infection extended into the pulmonary artery as an (3) arteritis. The high coagulability of the venous blood in the pulmonary artery accompanying the sepsis, together with a low blood pressure slowing the stream over a damaged artery lining, produced (4) a thrombus which was not extensive enough to cause death at that time. Later, after a good night's rest, with slowing of the blood stream during sleep (5) another thrombus formed.

and the symptoms appeared with the activity on awakening. (6) Death did not occur until the new portion had retrogressed far enough to occlude the larger pulmonary branches.

There was no attack of sudden pain, as is usual in cases of embolism, nor was any source for emboli found.

Had this patient lived longer, the complete syndrome on which the diagnosis of Ayerza's disease could be made might have developed—hypertrophy of the right side of the heart from the extra work thrown on it; polycythemia, from the demand for more oxygen carriers; sclerosis of the pulmonary artery; chronic cough; cyanosis, and later serious cardiac failure.

THE DYNAMICS OF THE CIRCULATION IN COARCTATION (STENOSIS OF THE ISTHMUS) OF THE AORTA OF THE ADULT TYPE

RELATION TO ESSENTIAL HYPERTENSION *

HERRMAN L. BLUMGART, M.D.

JOHN S. LAWRENCE, M.D.

AND

A. CARLTON ERNSTENE, M.D.

BOSTON

Coarctation of the aorta or stenosis of the aortic isthmus is of considerable interest, not only because of its rarity, but also because arterial hypertension is practically always present. Arterial hypertension exists above the level of the stenosis in this condition in the absence of renal lesions, arteriosclerosis or other complicating factors. The blood pressure below the level of the stenosis is much lower. Coarctation of the aorta, therefore, presents an unusual opportunity to compare in the same person the dynamics of the circulation in arterial hypertension as it exists above the coarctation with the dynamics of blood flow under lower pressure below the level of the stenosis.

Coarctation of the aorta has been diagnosed clinically in almost eighty patients, but no studies of the blood flow have hitherto been recorded. The purpose of this communication is to present the clinical observations in two patients with coarctation of the aorta, together with the oxygen capacity and content of the arterial and venous blood of the arms as compared to that of the legs, the tracings of the pulse of the carotid, brachial and femoral arteries, the blood pressure in the upper and lower extremities, the arteriolar pressure above and below the level of the stenosis, and measurements of the velocity of blood flow by the radioactive method above and below the coarctation of the aorta. The embryology, clinical observations, pathology and diagnostic

* Submitted for publication, Aug. 13, 1930.

* From the Medical Research Laboratories of the Beth Israel Hospital, the Thorndike Memorial Laboratory at the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

criteria have been admirably reviewed by King,[1] Blackford,[2] Hamilton and Abbott,[3] and Abbott,[4] and will not be repeated here.

REPORT OF CASES

CASE I.—*History.*—D. W., an unusually well developed white man, a teamster, aged 47, entered the hospital complaining of shortness of breath of four months' duration. The family and marital histories were irrelevant. Except for an acute left mastoiditis fifteen years previously, the patient had always felt well and had had no symptoms referable to the cardiovascular or other systems.

Five years previously, the patient had noted occasional cramps and increasing weakness of both legs. He had been able, nevertheless, to continue work as a teamster, lifting boxes that weighed from 150 to 200 pounds (68 to 90 Kg.) many times every day. Four months before entry, he had symptoms of acute bronchitis, remained in bed three days, and then attempted to work. Shortness of breath became progressively more marked, particularly on lifting heavy boxes and on walking quickly. The cough also became worse, with paroxysmal exacerbations at night. Eleven weeks before admission to the hospital, he observed the onset of conspicuous palpitation of the heart, and was forced to use three pillows at night. Nine weeks before entry, he noticed a viselike pressure that was referable to the upper part of the sternum. This sensation of pressure was aggravated by exertion, but it did not radiate and was never associated with actual pain. He had not noticed edema at any time. In spite of these symptoms, he continued to work, but finally, eight weeks before admission to this hospital, he was so troubled by dyspnea and weakness that he was forced to enter the Boston City Hospital. At that time physical examination showed essentially the same findings as those noted later, except that the skin and sclerae were subicteric, signs of fluid were present over the base of the right side of the chest, and medium and coarse râles were heard elsewhere over the lungs. The signs of congestive failure gradually disappeared, and after four weeks, the patient was able to leave the hospital.

Physical Examination.—Physical examination directly prior to our observations on June 3, 1929, showed an unusually well developed man. The pupils reacted normally. Ophthalmoscopic examination showed slight but definite arteriosclerosis of the retinal vessels. Heaving systolic pulsations of the carotid arteries were equally prominent in both sides of the neck. The right subclavian pulsation was greater than the left. No thrills were palpable over these vessels.

The thorax was symmetrical, normal in shape and expanded equally. Several tortuous, visibly pulsating vessels were noted over the back (fig. 1). There were

1. King, J. T., Jr.: Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, Arch. Int. Med. **38**:69 (July) 1926.

2. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

3. Hamilton, W. F., and Abbott, M. E.: Coarctation of the Aorta of the Adult Type: I. Complete Obliteration of the Descending Arch at Insertion of the Ductus in a Boy of Fourteen; Bicuspid Aortic Valve; Impending Rupture of the Aorta; Cerebral Death, Am. Heart J. **3**:381, 1928.

4. Abbott, M. E.: Coarctation of the Aorta of the Adult Type: II. A Statistical Study and Historical Retrospect of 200 Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, Am. Heart J. **3**:392, 1928.

no thrills or murmurs over these vessels. The percussion note and breath sounds over both lungs were normal. No rales were heard. The apex impulse of the heart was normal and was felt in the fifth interspace 11 cm. from the midsternal line. No thrills were present. Relative cardiac dulness extended 11 cm. to the left and 4 cm. to the right of the midsternal line. Supracardiac dulness measured 6 cm. A soft systolic murmur was heard over the mitral area, and a harsh systolic murmur was audible in the supraclavicular fossae, the axillae and over the great vessels of the neck, especially on the right. There were no diastolic murmurs, and there was no systolic murmur in the interscapular region. The

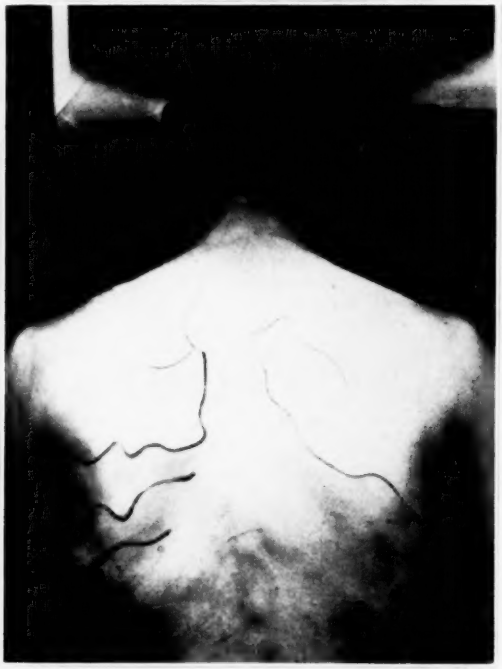

Fig. 1 (case 1).—Posterior view showing the superficial vessels of the collateral circulation. The course of the dilated, pulsating arteries has been outlined with a skin-marking pencil. The pulsations in these vessels were obliterated by pressure laterally on the subscapular arteries. The flow of blood evidently was backward toward the aorta.

radial pulses were equal, synchronous, bounding in quality, and of high tension. The vessel walls were slightly tortuous and thickened. The femoral arterial pulsations were feeble, and the popliteal and posterior tibial pulsations were barely palpable. Pulsation of the dorsalis pedis arteries could not be felt. Examination of the legs gave otherwise negative results.

Examination of the abdomen revealed no abnormalities except for a few superficial, dilated, pulsating arteries in the upper part of the abdominal wall. Pulsa-

tion of the abdominal aorta could not be felt. Rectal examination revealed nothing abnormal. The temperature, respiratory rate and pulse rate were normal during the period of observation. The patient weighed 71.8 Kg., and was 166 cm. in height.

Clinical Pathology.—Repeated urinalyses gave negative results. The red blood cells numbered 5,260,000 per cubic millimeter, and there was 90 per cent hemoglobin as measured by the Sahli method. The white blood cells varied from 6,200 to 10,500 per cubic millimeter, and the various types of cells occurred in normal proportions. The Kahn reaction of the blood was negative. The nonprotein nitrogen of the blood was 31 mg. per hundred cubic centimeters. The phenolsulphonphthalein excretion was 35 per cent in two hours and ten minutes.

Electrocardiograms.—Electrocardiographic tracings showed normal sinus rhythm, a rate of seventy per minute and left axis deviation. The duration of the

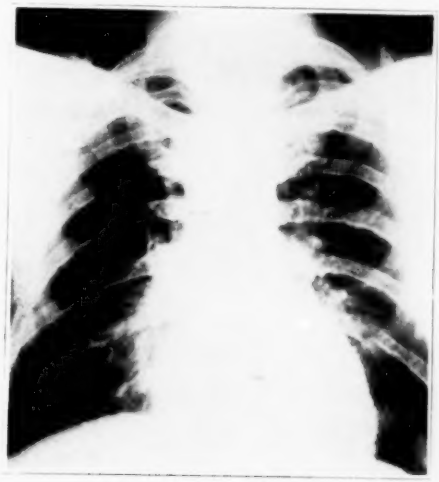

Fig. 2 (case 1).—Roentgenogram of the chest, showing the erosion of the lower borders of the ribs on both sides. The scalloping extends forward approximately to the posterior axillary line.

Q R S complex was 0.12 seconds, that of the P-R interval was 0.18 seconds. The T wave was diphasic in all leads. The Q R S complexes in leads II and III were notched.

Roentgenograms.—Roentgenographic films of the chest showed extensive irregularity of the inferior borders of the ribs posteriorly, extending forward approximately to the posterior axillary line (fig. 2). This deformity probably was due to erosion by the pulsating, tortuous vessels of the collateral circulation.[5] The cardiac measurements according to a roentgenogram taken at a distance of 7 feet (213 cm.)

5. Railsback, O. C., and Dock, W.: Erosion of the Ribs Due to Stenosis of the Isthmus (Coarctation) of the Aorta, Radiology **12**:58, 1929.

were normal. Examination of the skull showed no definite evidence of cranial or intracranial abnormalities. Fluoroscopy of the chest by Dr. Samuel A. Robins showed a moderate degree of emphysema. Forcible pulsations could be seen at the base of the heart and in the ascending portion of the aorta. These pulsations terminated in a narrow, triangular area situated posteriorly in the thoracic cavity at about the level of the angle of Ludwig. The descending portion of the aorta could not be made out definitely. The esophagus showed no abnormalities or transmitted pulsations.

Pulse Tracings.—Tracings of the cardiac impulse and the carotid, radial and femoral pulse waves were recorded with a Sanborn-Mackenzie polygraph. The radial pulse wave occurred approximately 0.25 seconds after the cardiac impulse and approximately 0.15 seconds after the carotid pulse wave. These time relationships may be considered normal. The femoral pulse wave, instead of preceding the radial pulse wave by from 0.01 to 0.02 seconds as normally, followed the radial pulse wave by approximately 0.15 seconds (fig. 3). There was characteristic flat-

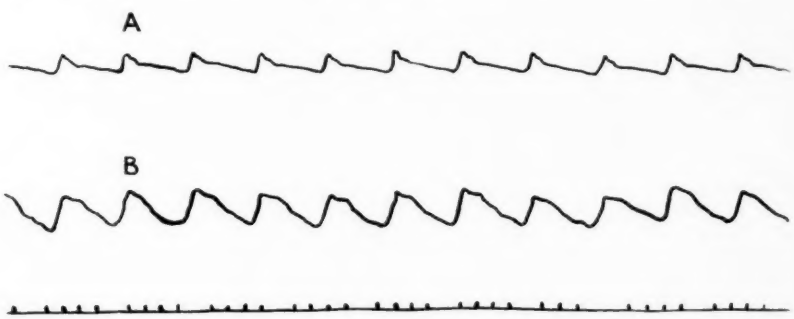

Fig. 3.—Simultaneous tracing of the radial (*a*) and femoral (*b*) pulse waves. A correction of —0.15 seconds is necessary for the time of onset of the femoral wave because of the difference in the length of the lever arms of the apparatus at the levels recorded on the tape. The femoral pulse wave occurs 0.15 seconds after the radial pulse wave.

tening and prolongation of the femoral wave due to the circuitous path that the pulse followed in reaching the femoral arteries.

Blood Pressure Measurements.—In the measurements of blood pressure, that of the right and left brachial arteries were equal and averaged 164 mm. of mercury systolic and 94 mm. of mercury diastolic. The standard mercury manometer with a cuff 14 cm. in width was used.

A special cuff, 20 cm. in width, was used in measuring the femoral blood pressure. The pressure was taken by auscultation over the popliteal artery with the cuff about the upper part of the thigh. The systolic pressure was 88 mm. of mercury and the diastolic, 76 mm. of mercury.

With a cuff about the calf of the leg and when the posterior tibial artery was palpated, the systolic pressure was 80.

Capillary and arteriolar pressures[6] were measured according to the method used by Lewis and Haynal[6a] and by Ellis and Weiss.[7] Open and closed capsules were used for the measurement of capillary pressure, and the closed capsule alone for arteriolar pressure. Over the sternum, the capillary pressue was 4 mm., and the arteriolar pressure 50 mm. of mercury. Over the lateral aspect of the upper part of the arm, the arteriolar pressure was 50 mm., and over the lateral aspect of the upper part of the thigh, 45 mm. of mercury.

Blood Volume Measurements.—The volume of the blood and of the plasma were measured by the brilliant vital red dye method used by Thompson.[8] The dye was injected into the right antecubital vein, and the sample of blood was taken from the femoral vein. The results are shown in table 1.

Blood Gas Measurements.—Duplicate measurements were made of the oxygen content and capacity of blood from the brachial artery, antecubital vein, femoral artery and femoral vein. The Van Slyke-Neill manometric apparatus[9] was used. The results are presented in table 2.

TABLE 1.—*Blood Volume Measurements in Case 1*

	Average Normal Values, Cc.	Observed Values, Cc.
Total plasma volume	3,550	3,460
Total blood volume	6,035	6,600
Plasma volume per kilogram	50	49
Blood volume per kilogram	85	93

6. By "capillary pressure" is meant the pressure necessary to cause minimal distinct blanching of the skin by compression of subpapillary venules.

By "arteriolar pressure" is meant the pressure transmitted to the subpapillary venules after dilatation of the arterioles and capillaries by histamine. The basis for believing that this pressure is due chiefly to arteriolar dilatation is presented by Lewis and Haynal. To what extent this pressure denotes the pressure in the "strongly muscled arterioles" cannot be stated since dilatation of the strongly muscled arterioles (the arched arterioles and the arterioles in the subpapillary network) and of the arterioles of the "minute vessels" (terminal arterioles) are important but indeterminate factors. Moreover, the degree to which these influences are opposed by capillary tone and frictional resistance cannot be stated precisely. As used in the present communication, the measurements of arteriolar pressure represent comparative values rather than quantitatively—precise measurements.

6a. Lewis, T., and Haynal, I.: Observations Relating to the Tone of the Minute Vessels of the Human Skin, with Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, Heart **14**:177, 1928.

7. Ellis, L. B., and Weiss, S.: The Measurement of Capillary Pressure under Natural Conditions and after Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J. Clin. Investigation **8**:47, 1929.

8. Thompson, W. O.: Studies in Blood Volume: I. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, J. Clin. Investigation **2**:477, 1926.

9. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

Blood Velocity Measurements.—The velocity of blood flow of the lesser and greater circulations was measured by the radioactive method.[10] At the time these measurements were made, the pulse rate averaged 60 per minute, and was not significantly altered by the technical procedure. The vital capacity of the lungs averaged 4.3 liters, or 2.4 liters per square meter of body surface, which is 96 per cent of the average for normal persons. A summary of the measurements of the velocity of circulation is presented in table 3.

CASE 2.—*History.*—T. M., a white man, aged 66, a retired freight handler, was referred to us through the courtesy of Dr. Henry A. Christian. He was first admitted to the Peter Bent Brigham Hospital in February, 1918, complaining of shortness of breath on slight exertion, cough and palpitation of about five years' duration. These symptoms had become progressively worse during the preceding three weeks. Physical examination revealed an enlarged heart with a blowing

TABLE 2.—*The Utilization of Oxygen in Two Resting Subjects with Coarctation of the Aorta*

	Subject D. W.	Subject T. M.
Brachial artery		
Oxygen content, per cent by volume	17.73	16.07
Oxygen capacity, per cent by volume	19.64	17.86
Percentage saturation	90.3	89.9
Antecubital vein		
Oxygen content, per cent by volume	16.11	9.71
Oxygen capacity, per cent by volume	19.83	17.85
Percentage saturation	81.2	54.4
Femoral artery		
Oxygen content, per cent by volume	17.74	
Oxygen capacity, per cent by volume	20.35	
Percentage saturation	87.2	
Femoral vein		
Oxygen content, per cent by volume	13.85	5.51
Oxygen capacity, per cent by volume	19.77	17.97
Percentage saturation	70.1	31.4
Arteriovenous difference		
Arm, per cent by volume	1.62	6.36
Leg, per cent by volume	3.89	10.56

systolic murmur over the entire precordium, auricular fibrillation, advanced generalized arteriosclerosis and the signs of infiltration of both apexes. Numerous fine and medium moist râles were heard everywhere over the chest, especially at the apexes. Tubercle bacilli were found in the sputum. A large, tortuous artery was noted in the right side of the neck and a similar though smaller one in the left side. The brachial blood pressure was 150 mm. of mercury systolic and 95 mm. of mercury diastolic. The diagnosis was chronic tuberculosis of the lungs, enlargement of the heart, myocardial insufficiency, auricular fibrillation and generalized arteriosclerosis. With rest in bed and the administration of digitalis, improvement was rapid; at the end of three weeks the patient was transferred to the state sanatorium. He remained there for eleven days and then decamped.

10. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow: I. The Method Utilized, J. Clin. Investigation **4**:1, 1927. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: VII. The Pulmonary Circulation Time in Normal Resting Individuals, ibid. **4**:399, 1927; X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, ibid. **5**:379, 1928.

From March, 1918, to January, 1930, the patient was admitted thirty times to the Peter Bent Brigham Hospital because of mild congestive heart failure and bronchitis that always subsided after a few weeks of treatment. In 1919, increased tortuosity and prominence of the subclavian and subscapular as well as of the radial, brachial and temporal arteries were noted. In October, 1922, tortuous pulsating vessels were observed, extending symmetrically from both axillae to the infrascapular and interscapular region. Further examination of the vascular system showed essentially the same findings as at the time of our observations, and therefore the diagnosis of coarctation of the aorta was made.

The patient was admitted to the Beth Israel Hospital on Jan. 6, 1930. Although he had dyspnea on slight exertion and a moderately severe cough, he had been

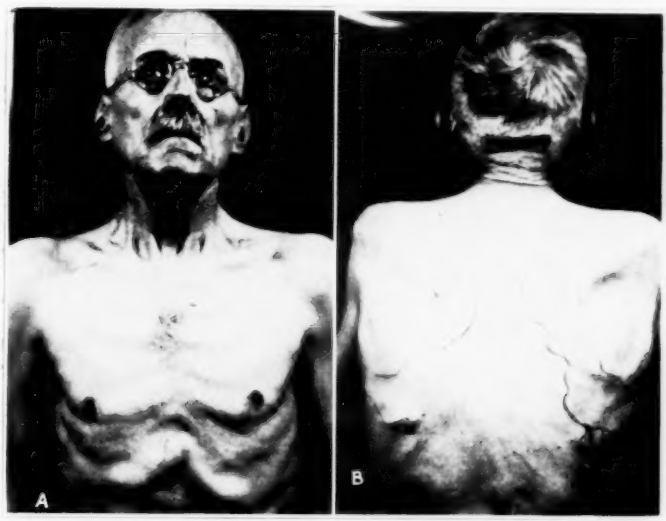

Fig. 4 (case 2).—*A*, showing the dilated arteries of the neck and anterior thorax; *B*, showing the superficial vessels of the collateral circulation.

feeling well. He had not worked for eight years. His feet had felt cold constantly for many years, and occasionally, at night, cramplike pains in the calves of the legs had troubled him.

Physical Examination.—Examination showed a well developed but undernourished white man propped up in bed on three pillows, coughing at frequent intervals, and raising a small amount of mucopurulent sputum. There was no respiratory discomfort between paroxysms of coughing. Both pupils were slightly irregular, and the left was larger than the right. Ophthalmoscopic examination revealed advanced tortuosity of the vessels with slight arteriovenous nicking. The lips were slightly cyanotic. The thorax was symmetrical, long and narrow and moderately flattened in the anteroposterior diameter. The infraclavicular and supraclavicular fossae were prominent. Expansion of the lungs was somewhat limited, but equal on the two sides. Hoover's sign was positive. The apex

impulse of the heart was felt in the fifth interspace, 10 cm. from the midsternal line. A coarse systolic thrill was felt over the entire precordium. Relative cardiac dulness extended 12 cm. to the left and 3.5 cm. to the right of the midsternal line. Supracardiac dulness measured 7 cm. On auscultation, a harsh, blowing, systolic murmur was heard over the entire precordium with points of maximum intensity at the apex and in the left second interspace. A murmur of similar quality was heard in the interscapular region. The heart rhythm was completely irregular; the rate was 56 per minute. There was dulness on percussion over both apexes of the lungs posteriorly and over the apex of the left lung anteriorly. Numerous persistent fine crepitant râles were heard over the upper part of the back and front of the chest. A few sibilant and sonorous râles were heard over various parts of the chest. All of the superficial arteries were markedly thickened and tortuous. Forcible pulsations were seen over the course of the transverse cervical and subclavian arteries in both sides of the neck and over the subclavian arteries in both infraclavicular fossae (fig. 4*A*). Systolic thrills and murmurs were present over these vessels. The subscapular arteries were dilated and easily palpable. On the right side of the thorax anteriorly, a small pulsating vessel was seen and felt over the costal cartilages of the seventh and eighth ribs (fig. 4*A*). Several pulsating, dilated arteries were seen and felt over both sides of the back, extending posteriorly from the subscapular artery (fig. 4*B*). The pulsation in the larger vessels could be obliterated by pressure on the subscapular artery. The radial pulses were small, equal, synchronous and completely irregular, and there was a deficit in the pulse rate of 4 or 5 beats per minute. On palpation, the pulse waves in the femoral arteries were approximately equal to those in the radial arteries, but the popliteal and dorsalis pedis pulses were barely perceptible. Neither posterior tibial pulse could be felt. Examination of the abdomen gave negative results. The pulsation of the abdominal aorta could not be felt. Rectal examination revealed moderate enlargement of the prostate. Examination of the extremities gave negative results except for a definitely subnormal temperature of the feet. Neurologic examination revealed no abnormalities. The temperature and the respiratory rate were normal during the patient's stay in the hospital. The patient weighed 57.5 Kg., and was 169 cm. in height. The vital capacity of the lungs was 1,800 cc.

Clinical Pathology.—The red blood cells numbered 4,640,000 per cubic millimeter, and there was 75 per cent of hemoglobin as measured by the Sahli method. The white blood cells numbered 6,900 per cubic millimeter. The differential count of the cells and the number of blood platelets were normal. The blood sugar and nonprotein nitrogen were within normal limits. The Wassermann reaction of the blood was negative. The urine was negative on repeated examinations. The phenolsulphonphthalein excretion was 40 per cent in two hours and ten minutes.

Electrocardiograms.—Electrocardiographic tracings showed auricular fibrillation, a ventricular rate of 60 per minute and intraventricular block of the right bundle branch type.

Roentgenograms.—Roentgenographic examination of the chest revealed coarse mottling throughout both upper lobes and small cavities in the apex of the right lung. The hilar regions were considerably increased in width and density. There was advanced erosion of the inferior borders of the ribs, extending forward approximately to the posterior axillary line (fig. 5). The cardiac measurements as shown by a roentgenogram taken at a distance of 7 feet (213 cm.) showed

moderate transverse enlargement of the heart. Fluoroscopic examination of the chest by Dr. Samuel A. Robins showed the transverse arch of the aorta somewhat pointed and incompletely visualized.

Pulse Tracings.—The radial pulse wave appeared approximately 0.05 seconds later than the carotid pulse wave and approximately 0.05 seconds before the femoral pulse wave. Normally, the femoral precedes the radial pulse wave by from 0.01 to 0.02 seconds.

Blood Pressure Measurements.—The blood pressure was approximately the same in both arms. The average of a series of measurements was 171 mm. of

Fig. 5 (case 2).—Erosion of the lower borders of the ribs.

mercury systolic and 96 mm. of mercury diastolic. On all occasions the systolic pressure measured by the palpatory method was only a few millimeters lower than by the auscultatory method.

The femoral systolic blood pressure was obtained by placing a special cuff, 20 cm. wide, about the middle of the thigh and palpating the dorsalis pedis artery. The average of a series of measurements was 123 mm. of mercury.

The capillary pressure over the sternum was 5 mm., and the arteriolar pressure, 50 mm. of mercury. Over the lateral aspect of the upper part of the arm and upper part of the thigh, the arteriolar pressure was 50 mm. of mercury.

Blood Gas Measurements.—Duplicate measurements were made of the oxygen content and capacity of blood from the brachial artery, antecubital vein and femoral vein. The results are presented in table 2.

CLINICAL CONSIDERATIONS

Diagnosis.—The diagnosis of coarctation of the aorta was established in both patients by (1) the presence of hypertension in the vessels of the arms as contrasted with the relatively low blood pressure in the legs; (2) the evidence of extensive collateral arterial circulation observed on physical examination and also made apparent by the erosions of the ribs seen in the roentgenograms of the chest, and (3) the diminution and retardation of the arterial pulses in the legs.

Presence of Other Congenital Anomalies.—Although the infantile form of coarctation of the aorta frequently is associated with other conspicuous congenital anomalies, the adult form is usually free from such gross abnormalities. Careful clinical search for developmental anomalies in our patients was without success, although one cannot state whether any minor abnormalities will be found eventually on postmortem examination.

Degree of Stenosis.—The anatomic degree of stenosis in our patients cannot be stated, but the numerous widely dilated collateral pulsating vessels, the lowered blood pressure in the legs and, in the first patient, the feeble pulsations of the femoral arteries indicated a moderate or extreme degree of coarctation. Abbott [4] stated that in 155 of the 200 cases analyzed by her, the lumen of the aorta was reduced to 6 mm. or less.

Collateral Circulation.—In both patients the pulsating vessels over the back, epigastrium and the lower anterior part of the thorax, together with the prominent subclavian and subscapular arteries, indicated that the collateral circulation was accomplished mainly by the following routes: (1) by anastomoses between the superior intercostal artery of the subclavian and the first aortic intercostal that arises from the aorta just below the site of the constriction; (2) by anastomoses between the aortic intercostals and the subscapular artery and its branches, particularly the circumflex scapulae, and (3) by the internal mammary arteries and their anastomoses with the aortic intercostals. The fact that the erosion of the inferior borders of the ribs observed in the roentgenograms of both patients extended only as far forward as the posterior axillary line suggests that the collateral channels between the internal mammary arteries and the aortic intercostals were not extensively developed. In neither patient could the deep epigastric arteries be felt. In the second patient, the prominent transverse cervical arteries indi-

cated that these vessels also played an important rôle in the collateral circulation, probably by way of the anastomoses of the posterior scapular with the subscapular and circumflex scapular arteries.

Cardiac Signs.—Abbott [4] found cardiac hypertrophy and dilatation in 150 of the series of 200 cases. It is not an essential feature, however, since patients have lived to the age of 92 with almost complete atresia of the aorta, but without hypertrophy and dilatation of the heart.[11] In our first patient the heart was of normal size, while in the second it was definitely enlarged. The first patient showed none of the characteristic vascular murmurs usually evident in coarctation of the aorta. The second patient, however, presented the following frequently observed findings: (1) a systolic murmur over the interscapular region similar to the murmur noted by King [1] in his four cases, and (2) a loud, harsh precordial murmur.

Relation between Coarctation of the Aorta and Circulatory Failure.—One hundred and forty-eight or 74 per cent of the patients in the cases analyzed by Abbott,[4] died before or during the fortieth year of life. Our patients did not experience their first symptoms until after the age of 40, and are therefore somewhat unusual in this respect. Throughout the period of growth, and in later years, the collateral circulation evidently had kept pace with the increasing demands. This extraordinary feature was emphasized by Hamilton and Abbott [3] and is the more exceptional in our patients in view of the nature of their work. In the first patient the sole manifestation of diminished flow of blood below the coarctation was the appearance of cramps in the legs on unusual exertion several times during the preceding five years. King's [1] first patient likewise had intermittent claudication and, like our patient D. W., did exceptionally heavy work. In our second patient, diminution of blood flow in the lower extremities was indicated by subnormal temperature of the feet and occasional nocturnal cramps in the legs.

In neither patient was the inception of congestive failure associated with any unusual strain. In the first patient, the initial symptoms were those of bronchitis. In the second patient, the relation of auricular fibrillation and pulmonary tuberculosis to the initial appearance of myocardial failure cannot be stated. In both patients the increased work of the heart for many years in the presence of arterial hypertension was probably the primary factor leading to cardiac failure.

Relation Between Arterial Pressure and Degree of Arteriosclerosis.—In patients with essential hypertension, arteriosclerosis appears early

11. Reynaud, A.: Observation d'une oblitération presque complète de l'aorte, suivie de quelques reflexions, et précedée de l'indication des fairs analogues, consignées dans les auteurs, J. hebd. de méd. **1**:101, 1828; quoted by Abbott (footnote 4).

and progresses rapidly. Whether this is due to the increased arterial pressure or to the underlying pathologic process is not clear. It is remarkable that, although arterial hypertension had presumably been present above the level of the coarctation in both of our patients for over forty years, physical examination and roentgen studies failed to disclose any perceptible difference in the degree of arteriosclerosis in the upper and lower parts of the body. In our first patient the radial arteries were thickened but soft and only slightly tortuous. Ophthalmoscopic examination showed only slight arteriosclerosis such as might be expected in a patient of his age without elevated blood pressure. In our second patient, advanced arteriosclerosis was present in all of the superficial peripheral arteries as well as in the retinal vessels.

CIRCULATORY MEASUREMENTS

Retardation and Diminution or Absence of the Femoral Pulse.—The retardation and diminution or absence of the femoral pulse are not constant either in their presence or degree. In our patients the time intervals between the apical cardiac impulse and the carotid and radial pulses as measured with the polygraph were within the limits of normal. The rise of femoral pressure, however, occurred 0.15 seconds after the rise of radial pressure in case 1 and 0.05 seconds later than the rise of radial pressure in case 2. Normally, the femoral pulse wave precedes the radial pulse by from 0.01 to 0.02 seconds. Retardation of the femoral pulse was observed also in the patient studied by Railsback and Dock,[5] who used Frank capsules. In their patient, the femoral arterial pulse followed the radial pulse by 0.02 seconds.

The amplitude of the femoral pulsation is affected not only by the degree of patency of the aorta, but also by the caliber of the collateral pathways and by the directness of the route taken by the blood back to the thoracic aorta. The most extreme cases of coarctation may be difficult to diagnose because the collateral circulation follows a relatively direct route through widely dilated vessels. The facts that the femoral systolic pressure in case 2 approached more closely the brachial arterial pressure and that the pulse wave was less retarded than in case 1 suggest freer communication between the upper and lower parts of the body in the former subject.

Arterial and Arteriolar Pressures.—Cardiac energy is transformed into (1) kinetic energy, or energy of flow and (2) potential or pressure energy. Other factors remaining constant, the greater the peripheral resistance, the higher the systolic and diastolic, and therefore the mean arterial, pressure. The elevated arterial pressure in essential hypertension is generally considered compensatory to maintain a normal blood supply

to the tissues in spite of the increased arteriolar resistance. The arteriolar pressure of both of our patients above the level of the coarctation was 50 mm. of mercury by the histamine flare method. This pressure is much lower than that found by Ellis and Weiss[7] in patients with essential hypertension with similar brachial arterial pressures, but is approximately the same as that observed by them in subjects with normal blood pressure. The results suggest that while increased peripheral resistance may, as in essential hypertension, be responsible for the high blood pressure above the coarctation, this increased resistance is due, not to increased arteriolar resistance, but rather to the resistance offered by the stenosed aorta and the collateral pathways. The normal arteriolar pressure observed in the arms is in accord with this hypothesis rather than with the existence of a reflex mechanism that might be expected to manifest itself by arteriolar constriction and an elevated pressure in the arterioles.

Below the level of the coarctation the arteriolar pressure measured over the lateral aspect of the upper part of the thigh was 45 mm. of mercury in case 1 and 50 mm. of mercury in case 2. These results are similar to those normally found in the leg. The mean femoral arterial pressure in the first patient was about 80 mm. of mercury. The normal arteriolar pressure of 50 mm. of mercury indicates a low gradient of pressure in the smaller arteries, the condition approaching that in the precapillary vessels of a normal person in whom the pulsation is markedly diminished, while the volume flow continues normally. The maintenance of normal arteriolar pressure in spite of the low femoral arterial pressure favors a normal gradient of pressure in the arterioles and minute vessels and a more adequate blood supply to the tissues. As will be seen later, the slow velocity of blood flow observed along the larger vessels, and the relatively normal oxygen content of the arterial and venous blood of the leg are in accord with this concept.

Blood Gas Measurements.—Normally, the oxygen capacity of arterial blood is about 20 per cent by volume. The blood contains about 19 per cent of oxygen by volume as it leaves the lungs, and is therefore 95 per cent saturated. In passing through the tissues, the blood loses about 5 per cent of oxygen by volume.

In the first patient, the oxygen saturation of the femoral arterial blood was less than the saturation of the brachial arterial blood. This may be due to the utilization of oxygen in the dilated capillary network traversed by the blood in the collateral pathways. The higher oxygen capacity of the femoral arterial blood suggests that slight concentration of the blood occurred in the dilated capillaries of the

collateral circulation. Comparable studies could not be made on the second patient because of lack of cooperation.

The utilization of oxygen in both patients was somewhat greater in the leg than in the arm, but in both subjects the arteriovenous difference in the leg was within the limits of normal.[12] This indicates that, in spite of the lowered arterial blood pressure in the leg, there was no significant reduction in the minute volume flow of blood through the capillaries of the lower extremities. A normal femoral arteriovenous oxygen difference could be accompanied by decreased minute volume blood flow only if the metabolic level of the legs of our patients were reduced more than seems possible. The occasional occurrence of intermittent claudication in the first subject and the complaint by the second

TABLE 3.—*The Velocity of Blood Flow in the Greater and Lesser Circulation in Case 1*

	Seconds
Pulmonary circulation time including time taken to course through the heart	11
Time from the left ventricle to femoral artery (estimated)	11
Time from the femoral artery to superficial veins of foot	32
Time from the superficial veins of foot to femoral vein	29
Time from femoral vein to right auricle of heart	9
Total circulation time	92

patient of coldness of the feet and nocturnal cramps in the legs indicate, however, that the functional circulatory reserve was limited in both.

Blood Plasma Volume.—The volume of blood plasma of our first patient was near the upper limits of normal.[13] A tendency toward an increased volume of plasma is to be expected in the presence of the numerous dilated collateral pathways of the blood.

Velocity of Blood Flow and its Relation to Other Measurements.—The following discussion relates mainly to the first patient because measurements of the velocity of blood flow could not be made in case 2 owing to lack of cooperation, and because measurements of the diastolic femoral arterial pressure could not be obtained. It is of considerable interest that the time necessary for the radioactive substance to travel from the heart to the femoral artery was eleven seconds, whereas the time necessary for the material to travel from the femoral vein to the

12. Harrison, T. R., and Pilcher, C.: Studies in Congestive Heart Failure: I. The Effect of Edema on Oxygen Utilization, J. Clin. Investigation **8**:259, 1930.

13. Thompson (footnote 8). Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

heart was only nine seconds. Normally, the velocity of blood flow in arteries is approximately twice that in veins.[10] The abnormally long time necessary for the radioactive material to reach the femoral artery again indicates the circuitous route traveled by the blood before reaching the lower extremities and the increased resistance it encountered in coursing through the collateral channels.

A period of thirty-two seconds was necessary for the blood to flow from the femoral artery to the superficial vessels of the foot, while twenty-nine seconds were necessary for the radioactive material to flow from a rather large vein on the dorsum of the foot to the femoral vein. This relative slowing of arterial blood flow in the lower extremities is due to the low gradient of pressure in the larger vessels of the legs.

The regulation of blood flow through the minute vessels of the body is at present but imperfectly understood. Normally, the blood pressure in the femoral artery is approximately the same as that in the brachial artery, while the "arteriolar pressure" (the pressure in the larger precapillary vessels) is approximately 50 mm. of mercury. The pressure in the veins is approximately zero. Under circumstances requiring augmented blood supply (exercise, etc.), the local increased flow in the legs is probably secured in part by dilatation of the precapillary minute vessels. This results in a higher pressure in at least the first portions of these vessels and an increased gradient of pressure between them and the veins. The difference between the resting arterial and arteriolar blood pressure, according to this hypothesis, is one of the factors in what may be termed the "local circulatory reserve" by means of which increase in local blood supply can be obtained to meet increased demands.

In the legs of patients with coarctation of the aorta, we have found the arteriolar pressure normal but the femoral arterial pressure greatly reduced. The decrease in the arterial-arteriolar difference in pressure indicates that this factor of the normal local circulatory reserve is diminished. Under these circumstances, the arteriolar pressure can be raised only by elevation of the femoral arterial pressure which in turn depends on the aortic pressure above the coarctation and ultimately on the ability of the heart to perform an increased amount of work. If the heart is unable to respond by raising the aortic pressure, the local supply of blood will not be sufficient to meet the increased demands.

It is not altogether surprising, therefore, that the first symptoms of a failing heart may appear in the lower extremities where the circulatory reserve previously has been encroached on. In our patients, as in others observed by King,[14] intermittent claudication, nocturnal cramps

14. King, J. T., Jr.: Personal communication.

and diminished temperature of the legs appeared at an appreciable interval before the more usual signs of circulatory insufficiency in the upper parts of the body. Such symptoms may therefore be the earliest indication of a failing heart in patients with coarctation of the aorta, and should call for effective treatment even before the appearance of dyspnea or other evidence of circulatory stasis.

SUMMARY AND CONCLUSIONS

1. Coarctation of the aorta presents an opportunity to compare in the same person the dynamics of the circulation in arterial hypertension above the point of constriction with the dynamics of blood flow under lower pressure below the level of the stenosis. The results of an extensive study of two patients with coarctation of the aorta are presented.

2. The diagnosis was established in both patients by (1) arterial hypertension in the arms as contrasted with the relatively low blood pressure in the legs; (2) evidence of extensive collateral arterial circulation observed on physical examination and also made apparent by the erosions of the ribs seen in the roentgenograms of the chest; and (3) diminution and retardation of the arterial pulses in the legs.

3. Although arterial hypertension presumably had been present above the level of the coarctation in both patients for over forty years, physical examination and roentgenographic studies failed to disclose any perceptible difference in the degree of arteriosclerosis in the upper and lower parts of the body.

4. The arteriolar blood pressure in the arms was normal. This suggests that while increased peripheral resistance may, as in essential hypertension, be responsible for the arterial hypertension above the coarctation, this increased resistance is due, not to increased arteriolar resistance, but rather to the resistance offered by the constricted aorta and the collateral pathways.

5. The velocity of blood flow in the larger arteries of the leg was reduced, and the arterial-arteriolar difference in blood pressure was greatly diminished. According to the measurements of oxygen in the blood, the blood supply to the tissues under resting conditions was nevertheless within the limits of normal.

6. The hypothesis that the small arterial-arteriolar difference in pressure in the legs represents an encroachment on what may be termed the local circulatory reserve is discussed. This condition is contrasted

with that above the level of the coarctation, where a marked difference in arterial-arteriolar pressure prevails.

7. Considerations are brought forward that suggest that symptoms of local circulatory insufficiency in the legs such as intermittent claudication and nocturnal cramps may be the earliest indication of a failing heart in patients with coarctation of the aorta, and should call for effective treatment, even before the appearance of dyspnea or any other evidence of circulatory stasis.

Since this paper was submitted for publication, both of our patients have died. The diagnosis of coarctation of the aorta was corroborated at necropsy in both, and the postmortem observations will be the subject of a separate communication.

Book Reviews

PRACTICAL RADIATION THERAPY. By IRA I. KAPLAN, B.S., M.D. Price, $6. Pp. 354. Philadelphia: W. B. Saunders Company, 1931.

If Kaplan had adhered strictly to his plan of describing only the actual methods of irradiation used by himself in his work at Bellevue Hospital and elsewhere in New York, his manual might be used with considerable confidence. In turning to cancer of the stomach or Gaucher's disease, one might disagree with the author, feeling that it would have been better to list these conditions as unsuitable for irradiation. Nevertheless, one would have to admit that the outlined treatment could probably do no harm, and it might be useful to know that at least one large clinic did attempt to treat patients with these conditions. Unfortunately, however, the author seems to have found it desirable to pad his book with extensive extractions from other texts and journals, and this has involved a good many frank mistakes, to say nothing of questionable judgments.

One expects mistakes in a first printing and is prepared to excuse them. I list below a few of the more obvious ones in this book, which will undoubtedly be corrected before a second printing:

Page 19: "Their (x-rays') path is not affected by the magnet, nor can they be reflected, refracted, or polarized."

If the clerical assistant who presumably had charge of the padding had enjoyed the most casual acquaintance with modern physical literature, this mistake could have been prevented. It is scarcely necessary to point out that the earliest work on refraction was published in 1896, and that reflection and polarization have long since been commonplace procedures in physical laboratories.

Page 23: "The rays of X-ray and radium may either stimulate, inhibit or destroy living tissues."

While this old dogma is perhaps not thoroughly disproved, it is, to say the least, controversial and should scarcely be reprinted without comment in a book dated 1931.

Pages 23 and 24: "In some cases the cells of a tissue are more affected by a given amount of energy of one range of wavelength than they are by the same amount of energy of another range of wavelength." and "Some respond . . . . in different ways, depending upon whether or not the radiation is so administered that a large intensity is coupled with a short period of exposure."

Many people believe that these ideas have been definitely disproved. It hardly seems wise to state only one side of such an important question.

Page 58: In listing the relative merits of valve tube and mechanical rectifier equipment, certain statements are made that were true a year or so ago, but were by no means true in January, 1931, the date of publication. Modern valve tubes will carry as heavy a current as the best mechanical rectifier machine, and automatic discharge devices have done away with the factor of persistent charge in the condensers. The most important advantage of valve tube equipment is not listed; that is, the fact that it is free from high frequency surges so that sphere gap readings really mean something is not mentioned.

Page 63: Modern valve tubes do not require a large amount of resistance in the sphere gap circuit.

Page 130: By far the most serious error that has come to my attention is the description of the Kienböck-Adamson method of treating ringworm of the scalp. The original articles are easily available in any medical library and will be found to stress the idea that treatments should be given to five points on the scalp. Overlapping of the doses used for contiguous areas is an essential part of the plan. Kaplan's abstractor consulted the "United States Army X-Ray Manual" instead of the original literature, and then misread the account in the

manual. As a result the reader is advised to divide the scalp into four areas for treatment applying the rays to one area at a time and shielding the other three with lead-rubber. It is extremely unlikely that Kaplan actually uses such a method in New York, because owing to the curvature of the skull it would be practically impossible to deliver a full epilating dose to the margin of an area without overexposing the center. It is easy to understand how a careless abstractor would misinterpret the sketches in the "United States Army X-Ray Manual" and would misread "shielding eyebrows, etc."

DIE ENTZÜNDLICHE GRUNDLAGE DER TYPISCHEN GESCHWÜRSBILDUNG IM MAGEN UND DUODENUM. By PROF. DR. G. E. KONJETZNY. Price, 18 marks. Pp. 155, with 72 illustrations, some in color. Berlin: Julius Springer, 1930. (Buchausgabe des gleichnamigen Beitrages in "Ergebnisse der inneren Medizin und Kinderheilkunde," volume 37.)

This is a monograph of 155 pages in which are excellently presented the results of the ten year study of ulcer by Konjetzny and his associates, particularly Kalima and Puhl. It begins with a concise review of the older theories of the etiology and pathogenesis of ulcer and then proceeds at once to the investigations carried out in their clinic at Kiel on fresh material obtained at the operating table and submitted to careful histologic study.

The first question asked is whether or not ulcer develops in a previously normal mucosa. It is answered in the negative. Erosions and acute ulcers always accompany chronic ulcers, and they occasionally produce the ulcer syndrome without the presence of a chronic ulcer. These erosions and acute ulcerations are due to an inflammatory process in the mucosa, a gastritis and duodenitis. The erosion develops as the result of polymorphonuclear infiltration just beneath the epithelial membrane. This cellular accumulation increases in size until the membrane is either ruptured or absorbed; an exudate then pours forth and an erosion is formed. Eosinophils and plasma cells slowly appear. The lesion then either heals or becomes more chronic. This process is excellently pictured.

The author then reproduces photographs of lesions, showing all stages of transition from the acute erosion just described to a chronic ulcer, apparently proving conclusively that the process begins in the mucosa and extends into the deeper layers. The entire development is attributed to an inflammatory reaction in which the vascular lesions do not play a rôle and in which peptic activity does not take part. A great deal of space is devoted to arguments on these points. The work is carefully and thoroughly done; the presentation is clear and concise; the illustrations are splendid, and the argument is logical.

In conclusion, Konjetzny discusses the matter of therapy and insists that the best treatment for ulcer is that directed toward the gastritis, rather than toward neutralization of the acid or the control of psychic factors. Surgical intervention should be used only in cases in which complications, such as acute or chronic perforation, hemorrhage and stenosis, have developed. A statement is not made as to the type of surgical intervention recommended, but one infers that subtotal gastrectomy is the procedure of choice. During the ten year period, Konjetzny operated on 28 per cent of the patients with ulcer coming under his care.

This epochal monograph is highly recommended to all students of gastric disease.

STOFFWECHSELKRANKHEITEN. By ERICH LESCHKE, M.D., Professor of Internal Medicine, University of Berlin. Paper. Price, 8 marks. Pp. 130. Dresden: Theodor Steinkopff, 1930.

This little book, which is one of a series prepared especially for the busy practitioner, contains in condensed, but well arranged form, an amazing amount of information. Some of this is more, some less, reliable. It would be impossible for a reader who was untrained in the field of metabolism to disengage theory from fact, speculation from knowledge. The author, particularly in the sections

dealing with therapeutics, adopts a naively uncritical attitude for one who ranks among the leaders in the field of metabolism and endocrinology. Thus, in the section on the treatment for obesity is the serious recommendation of the use by mouth of anterior lobe pituitary substance in pluriglandular combination with ovarian and testicular preparations. The author is one of many who in the reviewer's opinion confuse rather than clarify endocrine problems by resort to pluriglandular, in Leschke's case "plurivegetative," theorizing. It is not to be doubted that all of the glands of internal secretion are affected when one is diseased, but the same can be said of other organs, including the skin, the bones and the muscles. Nor is it to be disputed that functional irregularities of the autonomic nervous system are concerned in many of the disorders of metabolism, but it may be predicted that the primary abnormality in these disorders will be found to be considerably less complex than one would judge from such texts as this one. Certainly conceptions of pluriglandular disturbance have contributed scarcely at all to the advance of factual knowledge of endocrinology and metabolism, while great progress has been made through the separate study of individual processes and individual organs. It is of interest in this connection that epinephrine, thyroxin, insulin and parathormone, to mention only the glandular products of established potency, are developments of the research of a new continent where the authoritative publications in the field of metabolism and endocrinology have been comparatively free from speculation.

TREATMENT OF EPILEPSY. By FRITZ TALBOT. Price, $4. Pp. 266. New York: The Macmillan Company, 1930.

The author has been concerned for some time with the careful and controlled therapy of epileptic patients. In this he has become proficient, because he has understood the modern conception of human metabolism and has applied his knowledge in an attempt to check what is, at least theoretically, a disturbance of metabolism. Dr. Talbot completely reviews the theories as to the etiology of epilepsy, and summarizes in an excellent manner present conceptions. He stresses, naturally, the theories of disturbance in oxygenation, the acidbase equilibrium and the water content. All of these factors may, of course, be part of one underlying disturbance. There does not seem to be enough evidence, however, that in the epileptic patient there is an excessive amount of hydration, a deficiency in oxygen or a tendency to alkalosis. The greatest evidence for these factors as a basis is the therapeutic effect of their reversal. Dr. Talbot considers in great detail the practical application of the ketogenic diet. He leaves nothing of importance unwritten concerning that therapy. Any physician desiring to know the exact technic can find it in this book. The volume is highly recommended to all who are desirous of learning the modern therapy for epilepsy.

HUMAN BIOLOGY AND RACIAL WELFARE. Edited by EDMUND V. COWDRY, Professor of Cytology, Washington University, St. Louis. Price, $6. Pp 612. New York: Paul B. Hoeber, Inc., 1930.

Twenty-seven contributors of recognized authority in their chosen fields have cooperated remarkably well in developing what amounts to a survey course in "human biology" for students, especially medical, and for mature lay readers. The need for such an integration of the many special sciences involved in the complete study of man is charmingly set forth in the keen analysis by Edwin R. Embree, who wrote the introduction. The book proceeds in logical steps from the astronomical consideration of life through the origin and evolution of man, his internal and external adjustments, including such topics as climate, food, urban and rural environment, antisocial behavior, disease, science and industry, and education. The future of man is treated in relation to the inheritance of disease, the biology of populations, the mingling of races, the purposeful improvement of the race and the intentional shaping of human opinion. The vast scope of this book

is evident. Throughout the various chapters runs a true scientific spirit by means of which facts and opinions are kept sharply separated. There is a wealth of information and wisdom to be gleaned, particularly if the reader takes advantage of the selected bibliography. The illustrations are excellent. The style is generally good and the diction always intelligible. It is a pleasant surprise to note how well the scientific contributors have presented their material in a popular style without excessive simplification. This volume hits fairly close to the mark of its purpose.

SBORNIK PRACI NA POCEST SEDESATYCH NAROZENIN. Dedicated to PROF. LADISLAV SYLLABY. By his pupils and friends. Pp. 848. Prague, 1928.

This book, in the spirit of a Festschrift, is dedicated to Prof. Ladislav Syllaby, professor of the "Karlova Universita" in Prague, on the occasion of his sixtieth anniversary.

The book contains forty-nine articles written by his pupils and friends in various European countries. At the end of the book there is a bibliography of the writings of Syllaby and his pupils.

The following are some of the important topics taken up in this book: Cytomorphologic Examination of Blood in Patients with Schizophrenia, by G. Altschuller and O. Janota; Diagnosis of Active Tuberculosis by Means of Fixation Reaction, by J. Jedlicka; Relation Between Lipocytal Coefficient and Osmotic Resistance of Erythrocytes, by V. Jedlicka; Comparative Study of Subcutaneous Fat and of Bone-Marrow Fat, by B. Kadlec; Medical Treatment of Gastric and Duodenal Ulcer, by H. MacLean; Posterior Cervical Lymphatic Syndrome in Cases of Chronic Cervical Arthritis, by J. A. Barre.

GRENZ RAY THERAPY. By GUSTAV BUCKY, M.D. Price, $3.50. New York: The Macmillan Company.

The author describes the physical and physiologic characters of "Grenz" or borderline rays so named because they lie in the spectrum at the lower limit of the roentgen rays. Their wavelength is from 1 to 3 Angström units. In penetrability they are so soft that their absorption in air is appreciable. Their therapeutic use is therefore limited to superficial lesions of the skin and to certain systemic diseases in which an erythema acts favorably.

No extravagant claims are made as to the curative effect of the rays. Preliminary reports are made in a considerable list of diseases of the skin in which the results of other radiotherapy are already known. In a goodly number of these, excellent results are claimed. Another list names conditions in which good results were obtained. In a third list bad results are acknowledged.

The Grenz rays are said to present less dangers than the roentgen rays in that cumulative effects are absent and superficial burns heal easily.

HYPERTENSION. By LESLIE T. GAGER, M.D., Clinical Professor of Medicine in the George Washington University, Washington, D. C. Price, $3. Pp. 158. Baltimore: Williams & Wilkins Company, 1930.

An excellent and interesting discussion of hypertension is to be found in this monograph. The facts are stated clearly, concisely and accurately. Speculation is reduced to the minimum. The important references are quoted in extenso, so that it is scarcely necessary to go back to the sources. Symptomatology is skilfully delineated with the help of case histories. The chapter on the clinical study of hypertension may well be read over and over again. The author's emphasis on the study of the eyegrounds as the first approach after a careful history and general physical examination indicates his thorough familiarity with hypertension. A complete schema for the clinical study of patients with hypertension is given at the end of this chapter. Prognosis and treatment are discussed along conservative lines. This is an ideal book for medical students of the more intelligent type and for general practitioners who are still curious about disease.

THE CHEST IN CHILDREN. By E. GORDON STOLOFF, M.D. Price, $15. Pp. 432. New York: Paul B. Hoeber, Inc.

As an atlas portraying roentgenograms with full descriptions and systematic discussions this book is most creditable, outclassing previous works on this topic in the roentgen literature and equaling the best atlases on other roentgen subjects. While the major number of diseases considered are parallel to conditions also found in the adult and are modified only in their interpretation by the immature anatomy of the child's chest, considerable space is given to conditions most commonly found at an early age as well as those peculiar to childhood. Its illuminating treatment of the whole category of diseases of the chest gives the book instant and lasting appeal not only to the specialist in pediatrics and the roentgenologist but also to the general practitioner who has learned the unusual value of roentgen diagnosis afforded in so many diseases of the chest.

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $7.00; Canadian, $8.50; foreign, $9.50. Single copies, 25 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $12.00; Canadian, $12.50; foreign, $12.75.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn St. CHICAGO

CONTENTS

PAGE

NATURE OF THE SYMPTOMS ASSOCIATED WITH ESSENTIAL HYPERTENSION. DAVID AYMAN, M.D., AND JOSEPH H. PRATT, M.D., BOSTON 675

THE GAIN IN BODY WEIGHT ASSOCIATED WITH REMISSIONS IN PERNICIOUS ANEMIA. JANET M. VAUGHAN, B.M., B.CH. (OXFORD), LONDON, ENGLAND 688

THE AVERAGE DAILY ELIMINATION OF UROBILINOGEN IN HEALTH AND IN DISEASE, WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA: STANDARDIZATION OF METHOD BASED ON MESOBILIRUBINOGEN (H. FISCHER). C. J. WATSON, M.D., MINNEAPOLIS 698

CENTRAL VASOMOTOR IRRITABILITY: CONTRIBUTION TO THE PROBLEM OF ESSENTIAL HYPERTENSION. W. RAAB, M.D., VIENNA, AUSTRIA 727

SERUM AND PLASMA BILIRUBIN: A COMPARATIVE QUANTITATIVE STUDY OF ONE HUNDRED CASES. MENDEL JACOBI, M.D.; REUBEN FINKELSTEIN, M.D., AND RUDOLPH KURLEN, BROOKLYN 759

THE FECES OF PATIENTS WITH CHRONIC ARTHRITIS. ROBERT T. MONROE, M.D., AND FRANCIS C. HALL, M.D., BOSTON 764

THE TREATMENT OF PERNICIOUS ANEMIA WITH DESICCATED HOG'S STOMACH. PROF. I. SNAPPER, M.D., AND J. D. G. DU PREEZ, M.D., AMSTERDAM, HOLLAND 771

CARBOHYDRATE METABOLISM IN HYPERTENSION. MAX WISHNOFSKY, M.D., AND CHARLES S. BYRON, M.D., BROOKLYN 790

PROGRESSIVE THROMBOSIS OF THE PULMONARY ARTERY. CLARENCE H. BOSWELL, M.D., AND HAROLD D. PALMER, M.D., ROCKFORD, ILL. 799

THE DYNAMICS OF THE CIRCULATION IN COARCTATION (STENOSIS OF THE ISTHMUS) OF THE AORTA OF THE ADULT TYPE: RELATION TO ESSENTIAL HYPERTENSION. HERRMAN L. BLUMGART, M.D.; JOHN S. LAWRENCE, M.D., AND A. CARLTON ERNSTENE, M.D., BOSTON 806

BOOK REVIEWS 824